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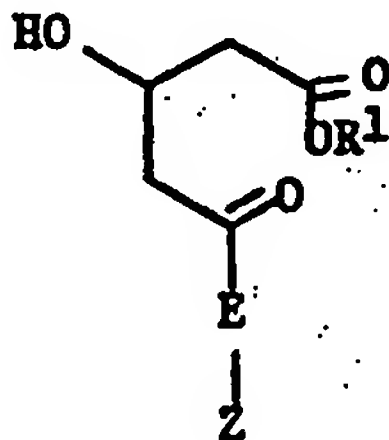
TITLE OF THE INVENTION

OXO-ANALOGS OF MEVINOLIN-LIKE ANTIHYPER-
CHOLESTEROLEMIC AGENTS

5 SUMMARY OF THE INVENTION

This invention is concerned with novel
compounds of structural formula I:

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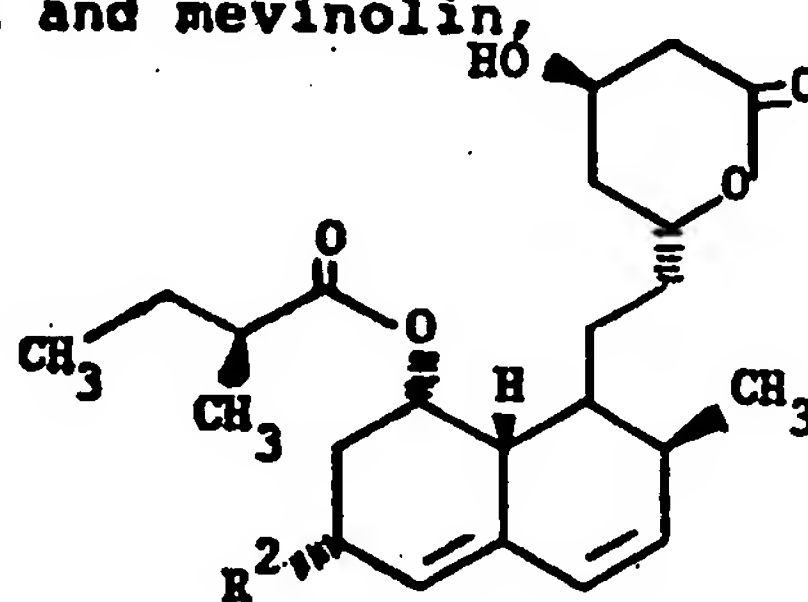


15 wherein Z is a variety of mono- and bi-carbocyclic
moieties with various substituents well known to
those skilled in the art of 3-hydroxy-3-methyl-
glutaryl Coenzyme A (HMG-CoA) reductase inhibitors
20 useful in the treatment of familial hyper-
cholesterolemia, hyperlipemia and atherosclerosis.

The invention is also concerned with novel processes for the preparation of the novel compounds; pharmaceutical formulations comprising a novel compound as active ingredient; and a method of
5 treating familial hypercholesterolemia, hyperlipemia, and atherosclerosis.

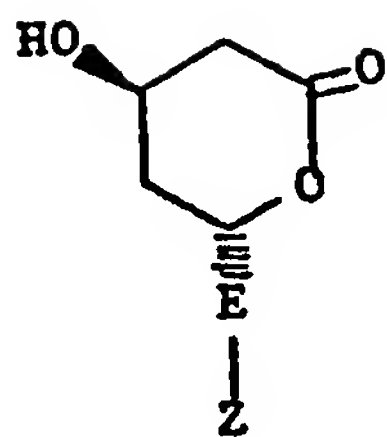
BACKGROUND OF THE INVENTION

Over the past several years a number of
10 structurally related antihypercholesterolemic agents acting by inhibition of HMG-CoA reductase have been reported in the patent literature and elsewhere. The compounds have varied from the natural fermentation
15 products, compactin and mevinolin,



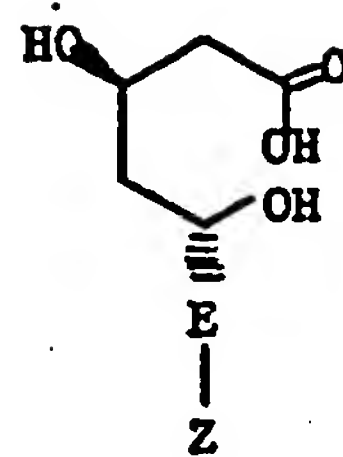
Compactin ($R^2=H$)
Mevinolin ($R^2=CH_3$)

25 to di- and tetrahydro derivatives thereof; to analogs with different esters in the 8-position of the polyhydronaphthalene moiety, to totally synthetic analogs, wherein the polyhydronaphthalene moiety is replaced by substituted mono- and bicyclic aromatics,
30 and biphenyls. But in all instances the active compound included a 4-hydroxytetrahydropyran-2-one ring or the corresponding 3,5-dihydroxy acid, or derivatives thereof, formed by opening the pyranone ring such as:



II

4-hydroxytetrahydropyran-2-one



IIa

3,5-dihydroxy-acid

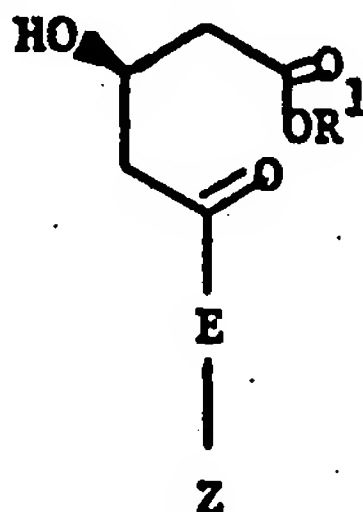
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- 10 In all of these compounds the 3,5-dihydroxy acid or corresponding lactone moiety is present and the particular stereochemistry depicted is essential for manifestation of the optimum enzyme inhibitory activity.
- 15 Now with the present invention there are provided compounds structurally related to those lactones and dihydroxy acids that do not have the 5-hydroxy functionality, do not form a lactone ring, and are incapable of stereochemical variation at the
- 20 5-position of the acid because the 5-carbon is not asymmetric. On the contrary, the 5-carbon carries an oxo function which greatly facilitates the total synthesis of active compounds in that by eliminating one asymmetric center it is unnecessary to separate
- 25 diastereoisomers or to conduct a stereoselective synthesis to obtain optimum enzyme inhibitory activity. It is believed that structures I are reduced in situ to generate the "active" inhibitors of structure II or IIa.
- 30 The active compounds of this invention are useful in either the racemic form or as the 3(R)-isomer. Those compounds produced by total synthesis are obtained initially as racemates, but

may be resolved by standard methods into 3(R)- and 3(S)-isomers. Compounds of Structure I which are synthesized starting from natural fermentation products such as mevinolin and its analogs are obtained as the optically pure 3(R)-isomers.

DETAILED DESCRIPTION OF THE INVENTION

The novel compounds of this invention have structural formula:

10



15

wherein

- R^1 is
- 1) hydrogen,
 - 2) C_{1-4} alkyl,
 - 3) 2,3-dihydroxypropyl,
 - 4) alkali metal cation, such as Na^+ , or K^+ , or
 - 5) ammonium of formula $NR^3R^4R^5R^6$ wherein R^3 , R^4 , R^5 and R^6 are independently hydrogen or C_{1-4} alkyl or two of R^3 , R^4 , R^5 and R^6 are joined together to form a 5 or 6-membered heterocycle such as pyrrolidino or piperidino with the nitrogen to which they are attached;

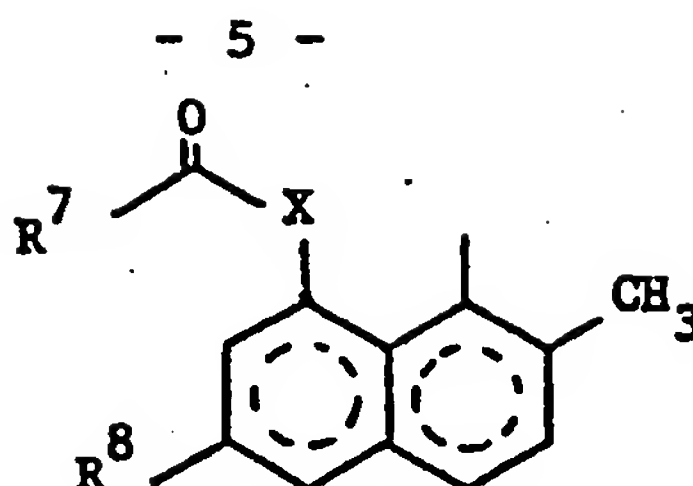
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30

E is - CH_2CH_2 -, - $CH=CH$ -, or $(CH_2)_3$ -; and

Z is 1)

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wherein the dotted lines represent all of the possible oxidation states of the bicyclic system such as naphthalene, dihydro-, tetrahydro-, hexahydro-, octahydro-, and decahydronaphthalene;

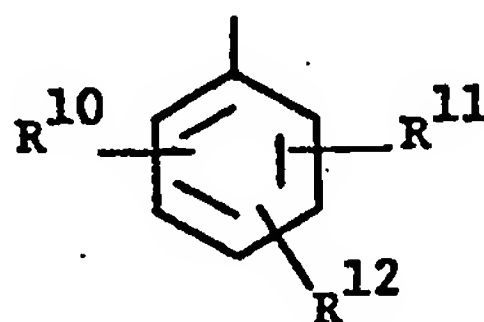
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X is -O- or >NR^9 wherein

15

R^9 is H or C_{1-3} alkyl;
 R^7 is C_{2-8} alkyl; and
 R^8 is H or $-\text{CH}_3$;

2)



20

wherein R^{10} , R^{11} and R^{12} are independently

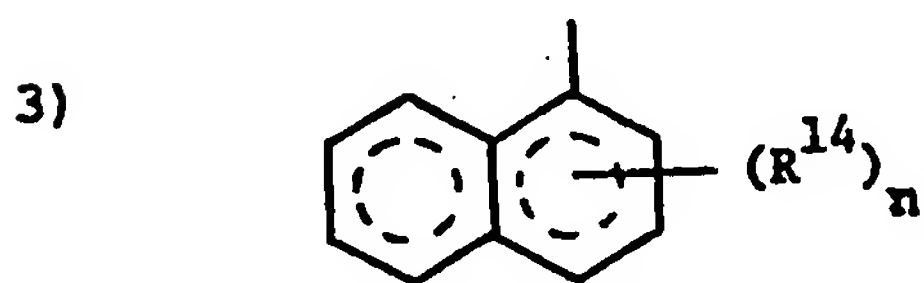
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- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C_{1-4} alkyl,
- d) halo- C_{1-4} alkyl,
- e) phenyl either unsubstituted or substituted with one or more of

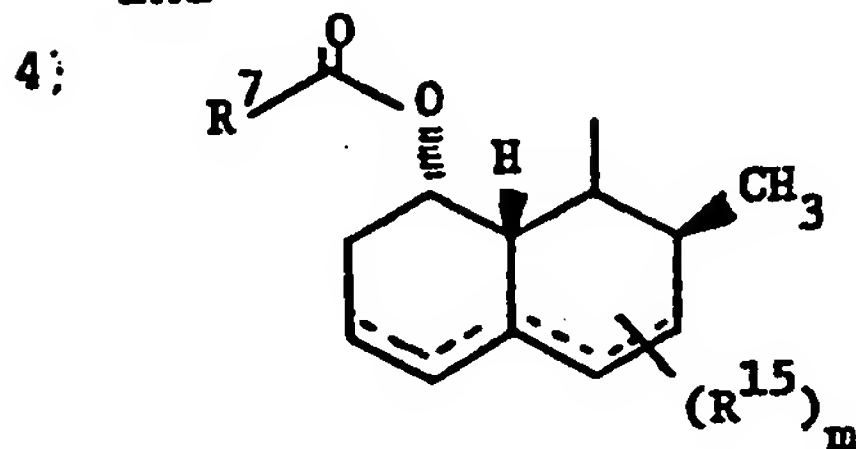
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- i) C_{1-4} alkoxy,
- ii) C_{1-4} alkyl,
- iii) C_{2-8} alkanoyloxy, or
- iv) halo- C_{1-4} alkyl,

- v) halo, such as bromo, chloro or fluoro,
 f) OR¹³ wherein R¹³ is
 i) hydrogen,
 ii) C₁₋₈alkanoyl,
 iii) benzoyl,
 iv) phenyl,
 v) halophenyl,
 vi) phenyl-C₁₋₃alkyl, either unsubstituted or substituted with one or more of halogen, C₁₋₄alkoxy, C₁₋₄alkyl or halo-C₁₋₄alkyl,
 vii) C₁₋₉alkyl,
 viii) cinnamyl,
 ix) halo-C₁₋₄alkyl,
 x) allyl,
 xi) C₃₋₆cycloalkyl-C₁₋₃alkyl,
 xii) adamantyl-C₁₋₃alkyl,



wherein n is 0-2, and R¹⁴ is halo such as chloro, bromo or fluoro, or C₁₋₄ alkyl, and



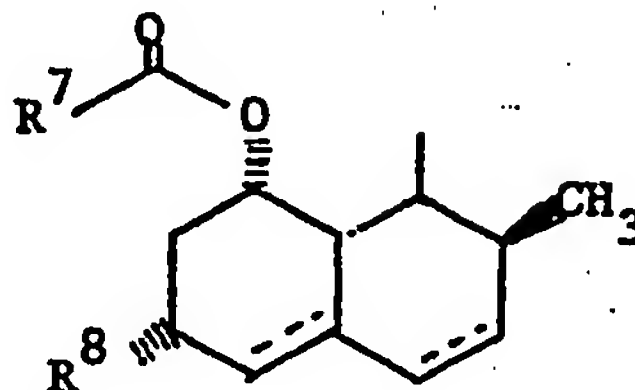
wherein the dotted lines represent possible double bonds there being 0, 1 or 2 double bonds; m represents 1, 2 or 3; and R^{15} is

- 1) methyl,
- 2) hydroxy,
- 3) C_{1-4} alkoxy,
- 4) oxo or
- 5) halo.

Preferred embodiments of the novel compounds are those in which: R^1 is hydrogen, an alkali metal cation or an ammonium cation;

E is $-CH=CH-$ or $-CH_2CH_2-$; and

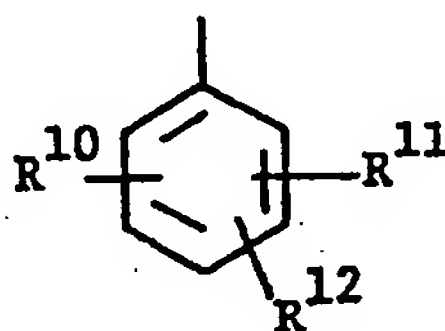
Z is 1)



wherein $R^7-\overset{\overset{O}{\parallel}}{C}-$ is 2-methylbutyryl or 2,2-dimethylbutyryl;

25

2)



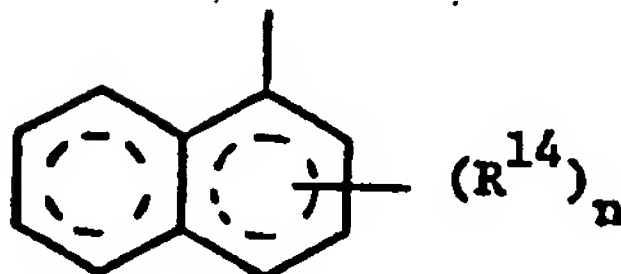
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wherein R^{10} , R^{11} and R^{12} are independently

- a) halogen,

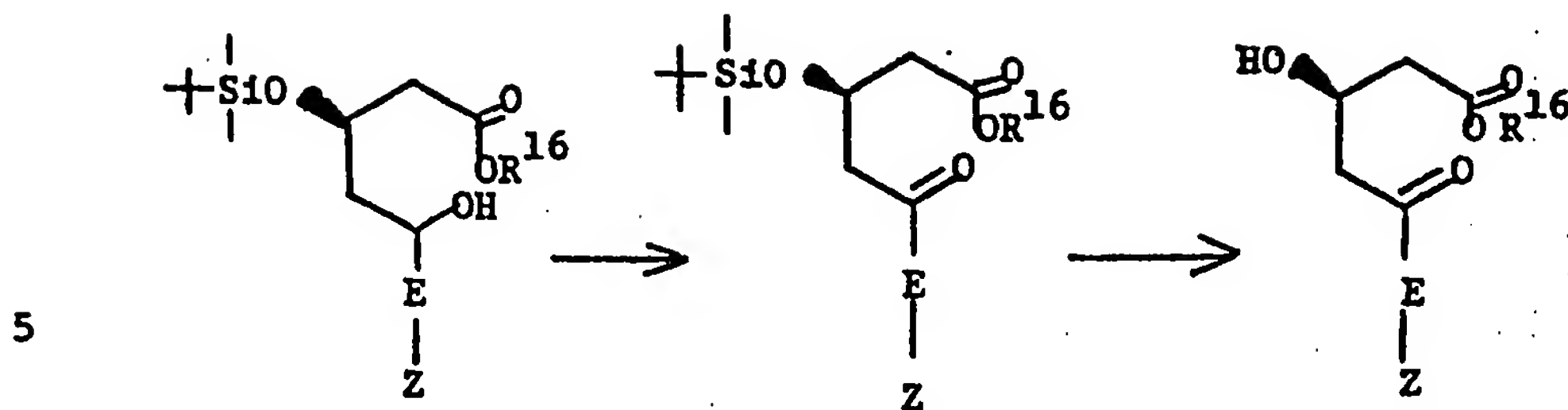
- b) C_{1-4} alkyl,
c) halo- C_{1-4} alkyl,
d) phenyl with 1 to 3 substituents selected
from halo, C_{1-4} alkyl or C_{1-4} alkoxy,
e) OR^{13} , wherein R^{13} is
i) phenyl,
ii) halophenyl,
iii) phenyl substituted with 1-3
substituents selected from
halogen, and C_{1-4} alkyl,
iv) phenyl- C_{1-3} alkyl, either
unsubstituted or substituted with
one or more of halogen, C_{1-4}
alkoxy, C_{1-4} alkyl or
halo- C_{1-4} alkyl; or

3)



wherein n is 0, 1 or 2 and R^{14} is methyl
and the ring system is naphthalene or 5,6,7,8-
tetrahydronaphthalene.

One novel process for preparing the novel
compounds of this invention is particularly useful
when starting with compounds with a pre-formed
4-hydroxytetrahydropyran-2-one moiety or the
corresponding 3,5-dihydroxy acid and is illustrated
as follows:



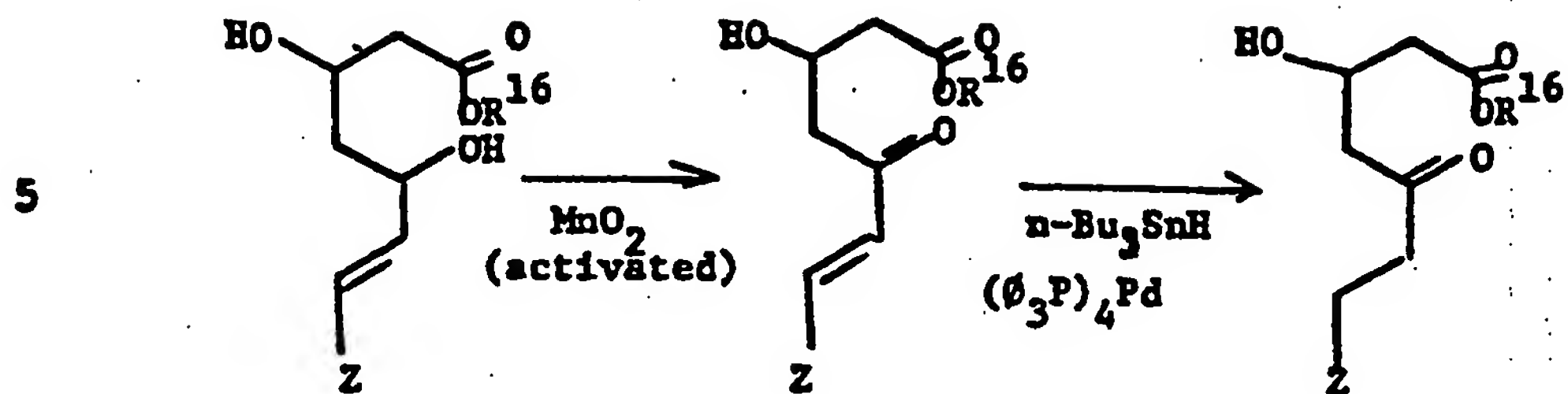
- 10 wherein R^{16} is C_{1-4} alkyl, especially methyl.
 After protecting the 4-hydroxyl of the lactone with a dimethyl-tert-butylsilyl group and preparing an alkyl ester by known procedures, the resulting 5-hydroxy of the open-chain acid is oxidized to the ketone.
- 15 Suitable oxidizing agents include: pyridinium chlorochromate in a chlorinated alkane such as methylene chloride or chloroform at about 0° to about 25°C for about 1 to 4 hour; oxalyl chloride in dimethylsulfoxide at about -70° to about -40°C for
- 20 about 0.25 to 0.5 hours; trifluoroacetic anhydride in dimethylsulfoxide at about -70° to -40°C for about 0.25 to 0.5 hour; and pyridinium dichromate in dimethyl formamide at 0° to 25°C for 1 to 8 hours.

The silyl ether group is then hydrolyzed by

25 treatment with acetic acid and tetrabutylammonium fluoride in tetrahydrofuran.

A related procedure is available for preparing compounds of this invention wherein E represents $-\text{CH}_2-\text{CH}_2-$. It obviates the need for

30 protection of the 3-hydroxy group before oxidizing the 5-hydroxy and is represented as follows:



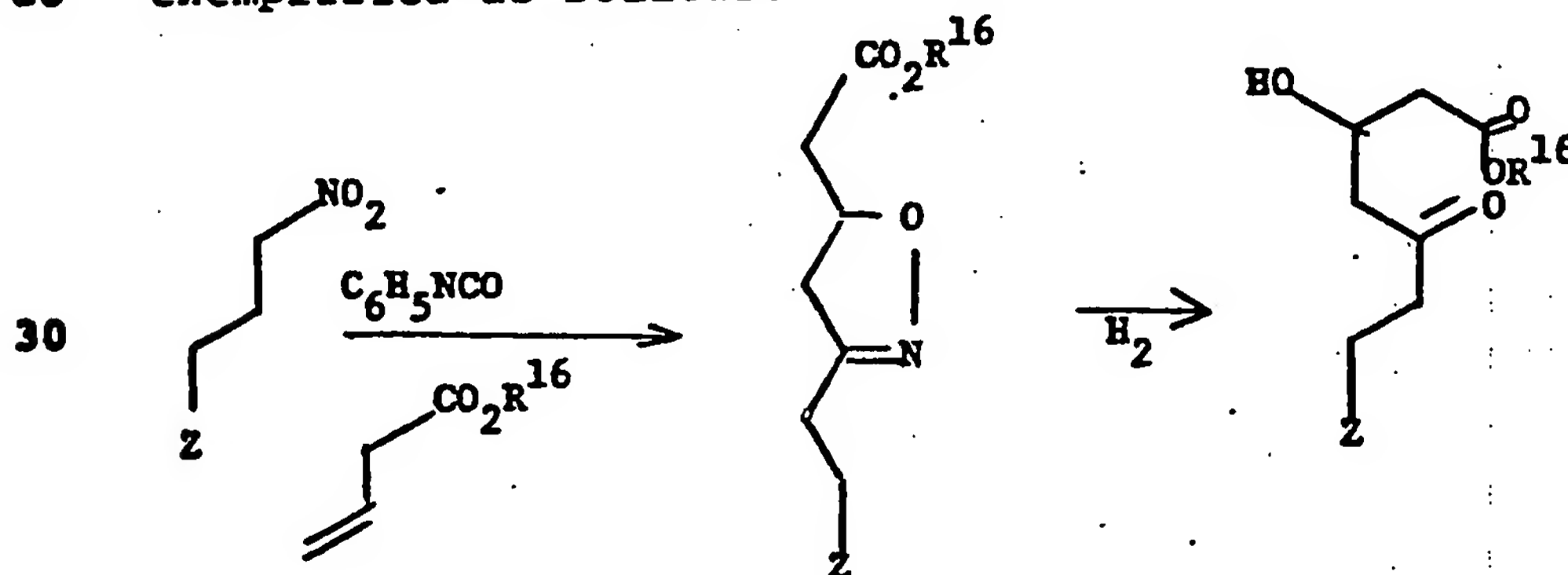
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In the first step the dihydroxy compound is treated with activated manganese dioxide in a chlorinated hydrocarbon such as chloroform, methylene chloride, 1,2-dichloroethane or the like at about 0°C to 40°C preferably at ambient temperature for about 15 to 30 hours. The 5-oxo compound produced is then treated with tri-n-butyltin hydride and tetrakis(triphenylphosphine)palladium(0) in an ethereal solvent such as ether, THF, 1,2-dimethoxyethane or the like, at about ambient temperature for about 15 to 30 hours.

20

Alternatively, if the 3-hydroxy-5-oxo-carboxylic acid moiety is being synthesized, the 5-oxo group is realized directly by a process which is another embodiment of this invention and which is exemplified as follows:

25



The nitro compound is treated with a C_{1-4} alkyl 3-butenate, preferably methyl 3-butenate, and an aromatic isocyanate such as p-toluoyl isocyanate, p-chlorophenyl isocyanate, phenyl isocyanate or the like, preferably the latter, and a bit of triethylamine as a catalyst in an inert organic solvent such as toluene, benzene, xylene, or the like at about 15 to 30°C, preferably about room temperature for about 5 to about 24 hours.

The resulting isoxazoline is reduced catalytically with palladium on carbon, platinum oxide or the like in an inert organic solvent such as a C_{1-3} alkanol, acetic acid or the like containing a little water in the presence of boric acid at about 15 to 30°C and about 1-2 atmospheres of hydrogen pressure for about 1 to 6 hours.

The ester resulting from either of the foregoing synthetic schemes is readily saponified to the corresponding carboxylic acid salt by treatment with aqueous alkali such as potassium, or sodium hydroxide to form the potassium or sodium salt respectively or with a quaternary ammonium hydroxide of formula $HONR^3R^4R^5R^6$ wherein none of the R groups is hydrogen to form the quaternary ammonium salt.

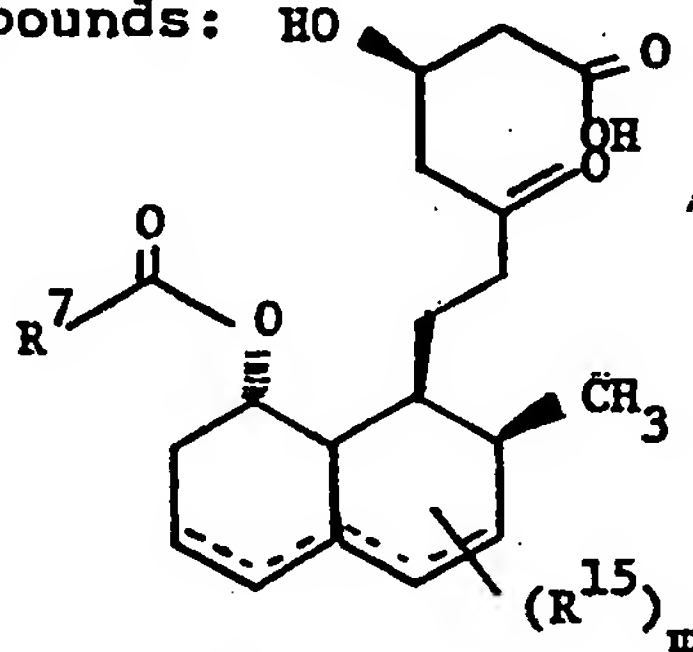
Acidifying any of these salts with a mineral acid results in the formation of the free carboxylic acid.

The acids are readily converted back to salts by treatment with the appropriate base or to esters by treatment with a C_{1-4} alkanol in the presence of a catalytic amount of an acid such as hydrogen chloride at about 50 to 100°C for about 3 to 6 hours.

The previously described salts are converted back to esters by treatment with an alkyl halide such as 2,3-dihydroxypropyl iodide in an aprotic solvent such as N,N-dimethylformamide, N-methylpyrrolidone or hexamethylphosphoramide at about 25 to 100°C for about 18 to 36 hours.

Those compounds, wherein Z is of the sub-type (4), i.e., in which the polyhydronaphthalene moiety is substituted with hydroxy or oxo, halo or alkoxy are prepared from the corresponding substrate in which the 5-oxo group of the heptenoic acid is already in place. The processes, as applied to the 5-hydroxy analogs or the corresponding lactones, are disclosed in EP application 76601, British patents 2,111,052 and 2,075,013, EP application 74222, and Japanese published applications J58010572 and J57155995. Using those processes there are produced the following compounds:

20



25

Double Bonds	R^7	$(R^{15})_m$
3,4:4a,5	1-methylpropyl	6-OH
3,4:4a,5	1,1-dimethylpropyl	6-OH
4,4a	1-methylpropyl	3-OH, 5-OH
4,4a	1,1-dimethylpropyl	3-OH, 5-OH
4,4a:5,6	1-methylpropyl	3-OH
4,4a:5,6	1,1-dimethylpropyl	3-OH
-	1-methylpropyl	6-OH

30

	-	1,1-dimethylpropyl	6-OH
	-	1-methylpropyl	3-OH
	-	1,1-dimethylpropyl	3-OH
	4,4a	1-methylpropyl	6-OH
5	4,4a	1,1-dimethylpropyl	6-OH
	4,4a	1-methylpropyl	3-OH
	4,4a	1,1-dimethylpropyl	3-OH
	4a,5	1-methylpropyl	6-OH
	4a,5	1,1-dimethylpropyl	6-OH
10	4a,5	1-methylpropyl	3-OH
	4a,5	1,1-dimethylpropyl	3-OH
	4,4a	1-methylpropyl	3-OH, 5=O
	4,4a	1,1-dimethylpropyl	3-OH, 5=O
	4,4a	1-methylpropyl	3=O, 5=O
15	4,4a	1,1-dimethylpropyl	3=O, 5=O
	-	1-methylpropyl	3-OH, 5-OH
	-	1,1-dimethylpropyl	3-OH, 5-OH
	4,4a	1-methylpropyl	3-Cl, 5-Cl
	4,4a	1,1-dimethylpropyl	3-Cl, 5-Cl
20	4,4a	1-methylpropyl	3-OCH ₃ , 5-OH
	4,4a	1,1-dimethylpropyl	3-OCH ₃ , 5-OH
	4,4a	1-methylpropyl	3-OC ₂ H ₅ , 5-OH
	4,4a	1,1-dimethylpropyl	3-OC ₂ H ₅ , 5-OH
	4,4a	1-methylpropyl	3-OC ₄ H ₉ , 5-OH
25	4,4a	1,1-dimethylpropyl	3-OC ₄ H ₉ , 5-OH
	4,4a	1-methylpropyl	6-CH ₃ , 3-OH, 5-OH
	4,4a	1,1-dimethylpropyl	6-CH ₃ , 3-OH, 5-OH

30 The novel pharmaceutical composition of this invention comprises at least one of the compounds of formula I in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated in a classical manner utilizing

solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations.

A typical capsule for oral administration contains active ingredient (25 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 25 mg of a water soluble salt of sterile active ingredient into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 ml of physiological saline, to produce an injectable preparation.

The novel method of treating atherosclerosis, familial hypercholesterolemia, or hyperlipemia of this invention comprises administration of an effective antihypercholesterolemic amount of a compound of Formula I to a patient in need of such treatment.

The dose to be administered depends on the unitary dose, the symptoms, and the age and the body weight of the patient. A dose for adults is preferably between 20 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1-4 times per day.

The compounds of this invention also have useful antifungal activities. For example, they may be used to control strains of Penicillium sp.,

Aspergillus niger, Cladosporium sp., Cochliobolus
miyabeorus and Helminthosporium cynodnotis. For
those utilities they are admixed with suitable
formulating agents, powders, emulsifying agents or
5 solvents such as aqueous ethanol and sprayed or
dusted on the plants to be protected.

This invention can be illustrated by the
following examples.

10

EXAMPLE 1

7-[2(S),6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-
1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-hydroxy-
5-oxoheptanoic acid

15

Step A: Preparation of 6(R)-[2-(8(S)-(2(S)-methyl-
butyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,
8a(R)-hexahydronaphthyl-1(S))-ethyl]-4(R)-
(dimethyl-tert-butylsilyloxy)-3,4,5,6-tetra-
hydro-2H-pyran-2-one

20

Mevinolin (4.04 g, 0.01 mol) was dissolved
in 25 ml of dry dimethylformamide (DMF) and treated
with 2.7 g (0.04 mol) of imidazole and 3 g (0.02 mol)
of dimethyl-tert-butylsilyl chloride, and the
solution was stirred under nitrogen overnight. The
mixture was poured into 200 ml of ether, washed with
25 2 X 50 ml of water, 1 X 25 ml of 1N hydrochloric
acid, 1 X 25 ml of saturated aqueous sodium carbonate
and 2 X 50 ml of brine, dried over $MgSO_4$ and
concentrated to dryness. The residue was chromato-
graphed on a "Still" column of silica gel (6.0 X 17.7
30 cm, 230-400 mesh) by elution with 45% ether in hexane
(V/V) collecting 20 ml fractions. The fractions
containing the product (21-52) were combined and
concentrated to dryness to give 5.2 of oil.

Step B: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-(tert-butyl-di-methylsilyloxy)-5(R)-hydroxyheptanoate

5 The silyl ether from Step A (1.03 g, 0.002 mol) was dissolved in 10 ml of methanol, treated with 2 ml of 1N aqueous sodium hydroxide and the mixture was stirred for 2 hours at room temperature. The methanol was evaporated under reduced pressure and
10 the residue was freed of water by azeotropic distillation of 4 X 10 ml of toluene. The solid residue was dissolved in 5 ml of dry DMF, treated with 300 μ l, (0.68 g, 0.0048 mol) of methyl iodide and the mixture was stirred overnight at room
15 temperature. The mixture was poured into 100 ml of ether and washed with 20 ml of water and 20 ml of brine, dried (MgSO_4) and concentrated to dryness to give 1.0 g of residue (contained DMF). This material was chromatographed on a "Still" column of silica gel
20 (6.0 X 17.7 cm, 230-400 mesh) by elution with 45% ether in hexane (V/V) collecting 20 ml fractions. Fractions 32-50 containing the major component were combined and concentrated to dryness to give 576 mg of oily product.

25

Step C: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-(tert-butyl-di-methylsilyloxy)-5-oxoheptanoate

30

The ester from Step B (586 mg, 0.001 mol) was dissolved in 10 ml of methylene chloride and cooled to 0°C. Pyridine chlorochromate (0.56 g, 0.0026 mol) was added and the stirred mixture was

allowed to warm spontaneously over 2 hours.

Additional pyridine chlorochromate (224 mg, 0.001 mol) was added and stirring was continued another hour. The methylene chloride was evaporated in vacuo. The residue was suspended in 5 ml. ether, placed on top of a 4 X 40 cm column of silica gel (70-230 mesh) and eluted with 40% ether in hexane (V/V) collecting 15 ml fractions. Fractions 10-23 were combined and concentrated to 130 mg. of oily product.

Step D: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-hydroxy-5-oxo-heptanoate

The silyl ether from Step C (230 mg, 0.00024 mol) was dissolved in 5 ml of tetrahydrofuran (THF) and treated with 54 μ l, (0.057 g, 0.00095 mol) of acetic acid and 710 μ l (1M in THF, 0.00071 mol) of

+ -
tetrabutylammonium fluoride ($\text{Bu}_4\text{N}^+\text{F}^-$) and the mixture was stirred overnight at room temperature.

+ -
Another 57 μ l of acetic acid and 710 μ l of $\text{Bu}_4\text{N}^+\text{F}^-$ were added and stirring was continued an additional 24 hours. The mixture was poured into 100 ml of ether and washed with 1 x 5 ml of 1N hydrochloric acid, 1 x 10 ml of saturated aqueous sodium bicarbonate and 2 x 10 ml of brine and dried (MgSO_4). Concentration to dryness gave 120 mg of an oil. The oil was chromatographed on a "Still" column of silica gel (1.5 x 17.7 cm, 230-400 mesh) by elution with 5% acetone in methylene chloride (v/v)

collecting 5 ml fractions. Fractions 12-20 containing the product were combined and concentrated to dryness to give 53 mg of solid (m.p. 64-66°C).

Recrystallization of a sample from hexane gave
5 material with m.p. 67-68°C.

Analysis for $C_{25}H_{38}O_6$ (434.55): Calc: C, 69.09;
H, 8.81.

Found: C, 69.30; H, 9.38.

10 Step E: Preparation of 7-[2(S),6(R)-Dimethyl-8(S)-
(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexa-
hydro-1(S)-naphthyl]-3(R)-hydroxy-5-oxohept-
anoic acid

The ester from Step D (43 mg, 0.0001 mol)
15 was dissolved in 5 ml of methanol and treated with 2
ml of 0.1N sodium hydroxide (0.0002 mol) and stirred
overnight at room temperature. The methanol was
evaporated in vacuo and the residue was acidified
with 1N hydrochloric acid and extracted with ether.
20 The ether extract was washed with 3 x 10 ml of brine
and dried over $MgSO_4$. Concentration to dryness
provided 36 mg of solid which after recrystallization
from ether/hexane had m.p. 102-103°C.

Analysis for $C_{24}H_{36}O_6$ (420.53): Calc: C, 68.54;
25 H, 8.63.

Found: C, 68.57; H, 8.88.

Employing the procedure substantially as
described in Example 1, Steps A through E, but
substituting for the mevinolin used in Step A,
30 equimolar amounts of the lactones described in Table
I there are produced the corresponding 5-oxo-
carboxylic acids, salts, and esters also described in
Table I in accordance with the following reaction
scheme:

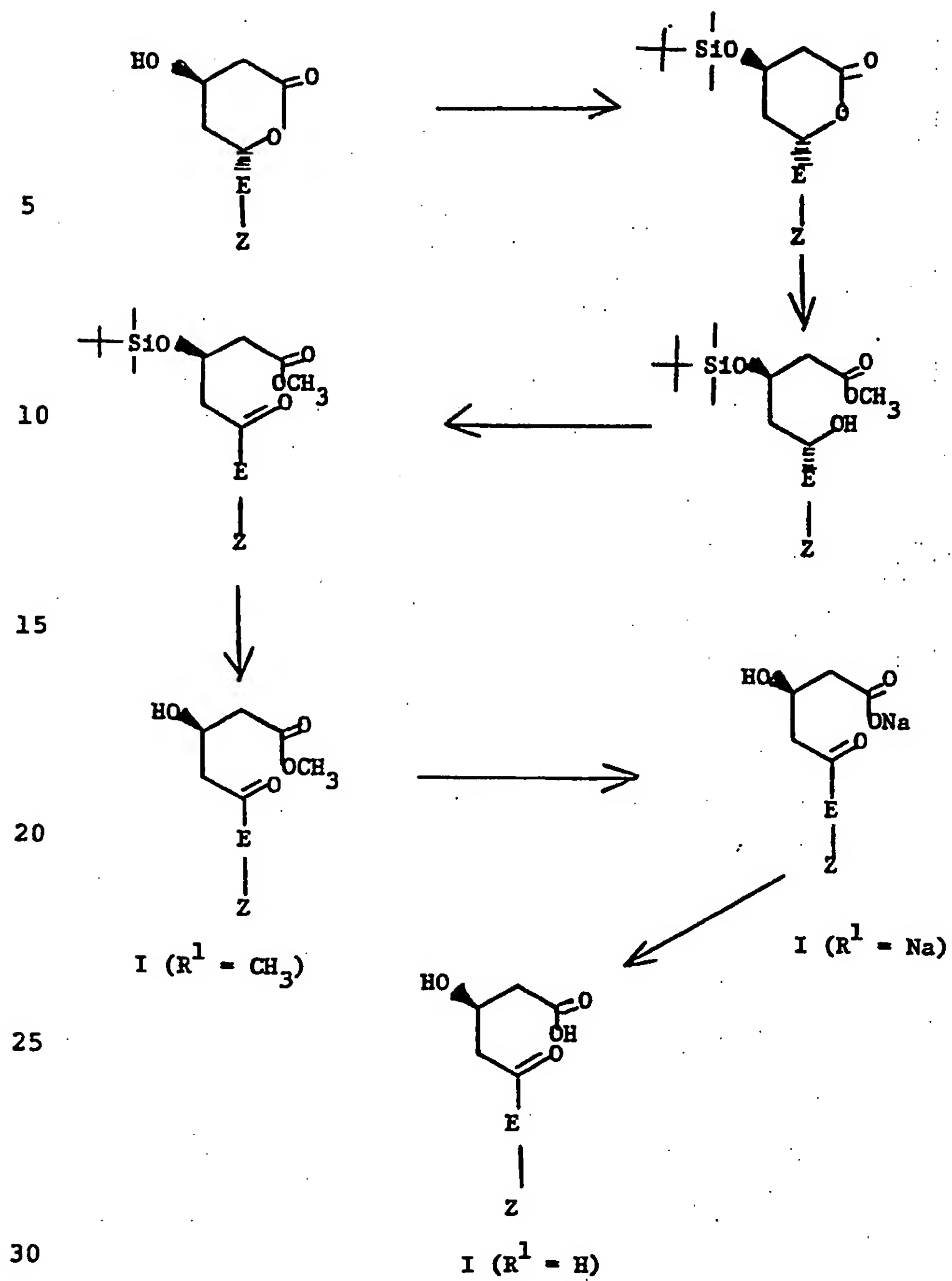


TABLE I

1)

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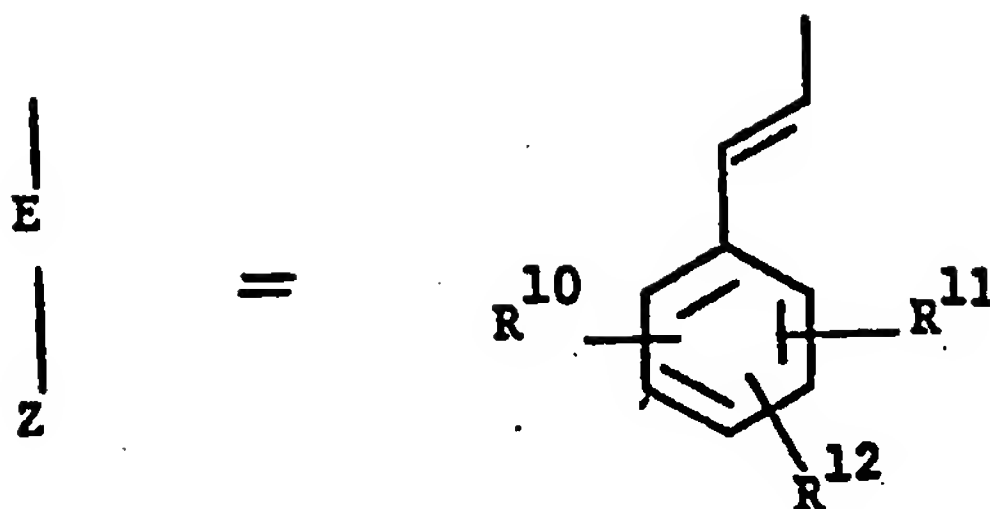
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	R^7	R^8	X	a	b
2(S)-methylbutyryl	-CH ₃	O	single	double	
2(S)-methylbutyryl	-CH ₃	O	single	single	
2(R)-methylbutyryl	-CH ₃	O	double	double	
2,2-dimethylbutyryl	-CH ₃	O	double	double	
2,2-dimethylbutyryl	-CH ₃	O	single	double	
2,2-dimethylbutyryl	-CH ₃	O	single	single	
acetyl	-CH ₃	O	double	double	
2(S)-methylbutyryl	H	O	single	single	
2,2-dimethylbutyryl	H	O	double	double	
2,2-dimethylbutyryl	H	O	single	single	
2,2-dimethylbutyryl	-CH ₃	NH	single	single	
2-methyl-2-ethylbutyryl	-CH ₃	NH	single	single	
2-methylbutyryl	-CH ₃	NH	single	single	
4-fluorobenzoyl	-CH ₃	NH	single	single	
4-fluorophenylacetyl	-CH ₃	NH	single	single	
4-tert-butylbenzoyl	-CH ₃	NH	single	single	
acetyl	-CH ₃	NH	double	double	
acetyl	-CH ₃	NCH ₃	single	single	
2,2-dimethylbutyryl	-CH ₃	NCH ₃	single	single	
2,2-dimethylbutyryl	-CH ₃	NH	double	double	

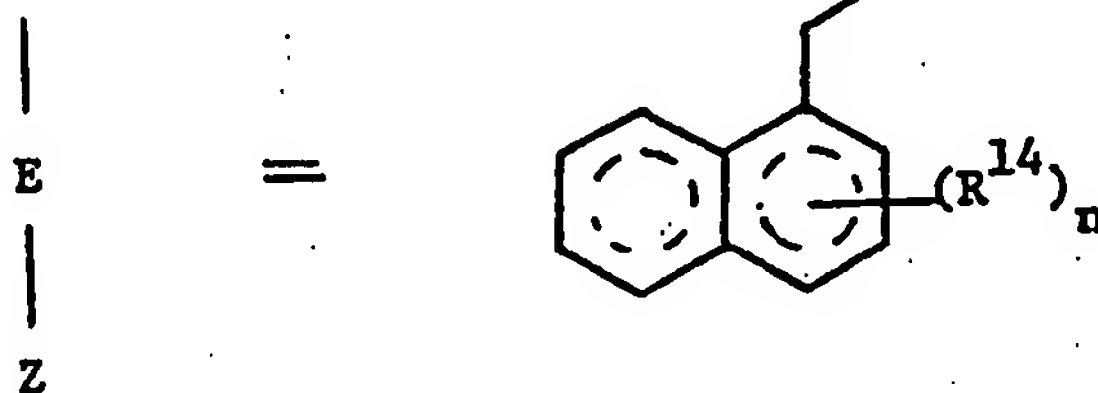
(2)



5

	R^{10}	R^{11}	R^{12}
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
10	6-(4-fluorophenyl)-	2-chloro	4-chloro
	6-(4-chlorophenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	4-methyl
15	6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
	6-(4-fluorophenyl)-	2-methyl	4-methyl
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
	6-(4-fluorobenzyloxy)	2-chloro	4-chloro
20	6-(4-fluoro-3-methylphenyl)	2-chloro	4-methyl

3)



25

	n	R^{14}	
30	1	2-methyl	naphthyl
	0	-	naphthyl
	2	2,6-dimethyl	naphthyl
	1	2-methyl	5,6,7,8-tetrahydronaphthyl

EXAMPLE 2

7-(4'-Fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoic acid

Step A: Preparation of Methyl 3-(4'-Fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)propionate

5

A solution of 1.716 g (13 mmol) of dimethyl malonate in 5 ml of DMF was added dropwise to a stirred suspension of sodium hydride (50% oil dispersion, 0.624 g, 13 mmol) in 15 ml of DMF and stirring was continued under nitrogen for 0.5 hour. The mixture was treated with ice bath cooling, with a solution of 3.1 g (11.8 mmol) of 2-chloromethyl-4'-fluoro-3,3',5-trimethyl-1,1'-biphenyl in 10 ml of DMF. The resulting mixture was stirred at 0°C for 10 minutes, at room temperature for 0.5 hour, and heated on a steam bath for 1 hour. Sodium chloride (0.759 g, 13 mmol) and 0.234 ml (13 mmol) of water were added to the reaction mixture and it was heated at reflux for 16 hours. The reaction mixture was cooled, poured into cold water and extracted with ether twice. The combined extracts were washed with dilute hydrochloric acid, dried over MgSO_4 , filtered and concentrated to dryness in vacuo to give 3.42 (11.38 mmol, 96%) of the desired product as a brown oil which was used directly in the next step without purification.

10

15

20

25

nmr (CDCl_3) δ : 2.27 (6H, a methyl singlet and a methyl doublet), 2.3 (2H, m), 2.34 (3H, s), 2.9 (2H, m), 3.60 (3H, s), 6.84 (H, bs), 7.1-7.2 (4H, m).

30

Step B: Preparation of 3-(4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)propanol

A solution of 3.42 g (11.4 mmol) of the ester from Step A in 25 ml of ether was added

dropwise to a stirred suspension of 0.38 g (10 mmol) of lithium aluminum hydride in 75 ml of ether at 0°C under nitrogen. After completion of the addition, the mixture was stirred at room temperature for 15 minutes, refluxed for 1 hour, cooled in ice and treated with successive additions of 0.4 ml of water, 0.35 ml of 20% (w/v) aqueous sodium hydroxide and 1.1 ml of water. The resulting mixture was stirred at 0°C for 0.5 hour, treated with anhydrous MgSO_4 , stirred for 15 minutes and filtered. The filtrate was concentrated in vacuo to give 3.08 g (11.3 mmol) (99%) of pale yellow oily product which was used directly in the next step without purification.

nmr (CDCl_3) δ : 1.45-1.7 (2H, m), 2.25 (6H, s), 2.33 (3H, s), 2.45-2.7 (2H, m), 3.45 (2H, t, $J=6\text{Hz}$), 6.85 (H, bs), 6.95-7.2 (4H, m).

Step C: Preparation of 2-(3-Bromopropyl)-4'-fluoro-3,3',5-trimethyl-1,1'-biphenyl

A solution of 1.08 g (4 mmol) of PBr_3 in 10 ml of ether was added dropwise to a stirred solution of 3.08 g (11.3 mmol) of the alcohol from Step B in 40 ml of ether at 0°C. The mixture was stirred at room temperature for 1 hour, refluxed for 0.5 hour, cooled to room temperature, poured into ice water and extracted with ether. The extract was washed with water and saturated aqueous sodium bicarbonate, dried over MgSO_4 , filtered and evaporated to dryness in vacuo. The residue was purified by flash chromatography on silica gel (230-400 mesh) by elution with methylene chloride/hexane (1:3, v/v). Combination and evaporation of the appropriate fractions gave the

desired bromide as a pale yellow oil, (1.9 g, 5.67 mmol, 48% overall Steps A, B and C).

nmr (CDCl_3) δ : 1.7-2.0 (2H, m), 2.27 (6H, a methyl singlet and a methyl doublet), 2.35 (3H, s), 2.55-2.8 (2H, m), 3.23 (2H, t, $J=6\text{Hz}$), 6.85 (H, bs), 6.95-7.2 (4H, m).

Step D: Preparation of 4'-Fluoro-3,3',5-trimethyl-2-(3-nitropropyl)-1,1'-biphenyl

10 A solution of 1.90 g (5.66 mmol) of the bromopropyl compound from Step C in 5 ml of ether was added to a stirred suspension of 1.31 g (8.5 mmol) of silver nitrite in 5 ml of ether at 0°C . The resulting mixture was stirred under nitrogen at 0°C for 7 hours, warmed to room temperature and stirred for an additional 16 hours. Another 1.0 g of silver nitrite was added and stirring was continued for another 20 hours.

20 The reaction mixture was filtered and the filtrate was concentrated to leave a residue which was purified by flash chromatography on silica gel (230-400 mesh) by elution with methylene chloride/hexane (1:4, v/v) to give, first, the recovered starting bromide, then the desired product, (0.64 g, 2.12 mmol, 78%). nmr (CDCl_3) δ : 1.8-2.2 (2H, m), 2.30 (6H, a methyl singlet and a methyl doublet), 2.33 (3H, s), 2.5-2.7 (2H, m), 4.18 (2H, t, $J=6\text{Hz}$), 6.88 (H, bs), 7.0-7.2 (4H, m). IR (neat) 1550, 1500 cm^{-1} .

Step E: Preparation of Methyl 3-[2-(4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)ethyl]-4,5-dihydro-5-isoxazoleacetate

5 A solution of 0.1 g (1.0 mmol) of methyl 3-butenate and 0.174 ml (1.6 mmol) of phenyl isocyanate in 1 ml of toluene was added with stirring to a solution of 0.240 g (0.8 mmol) of the nitropropyl compound from Step D and 2 drops of triethylamine in 1 ml of toluene. The resulting mixture was
10 stirred at room temperature for 3 hours. Additional quantities of methyl 3-butenate (0.1 ml), triethylamine (0.1 ml) and phenyl isocyanate (0.15 ml) were added successively and stirring was continued overnight (18 hours). The mixture was filtered and the
15 filtrate was concentrated in vacuo to a residue which was purified by flash chromatography on silica gel (230-400 mesh), first being eluted with methylene chloride to remove the impurities. Continued elution with acetone/methylene chloride (1:50, v/v) gave the
20 desired product (0.218 g, 0.57 mmol, 71%) as a pale viscous oil. nmr (CDCl_3) δ : 2.28 (6H, s), 2.32 (3H, s), 2.2-3.0 (6H, m), 3.70 (3H, s), 4.6-5.0 (H, m), 6.85 (H, bs), 7.0-7.2 (4H, m). IR (neat) 1735 cm^{-1} . Analysis calculated for $\text{C}_{23}\text{H}_{26}\text{FNO}_3$: C 72.04;
25 H, 6.83; N, 3.65.
Found: C, 72.35; H, 6.99; N, 3.88.

Step F: Preparation of Methyl 7-(4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoate

30 A mixture of 0.1 g (0.26 mmol) of the isoxazoline from Step E, 50 mg of 10% palladium on carbon catalyst and 48 mg (0.78 mmol) of boric acid

in 3 ml of methanol and 0.3 ml of water was stirred under hydrogen (1 atmosphere) at room temperature for 2.5 hours. The mixture was filtered and the filtrate was poured into brine and extracted with ether. The
5 ethereal extract was washed with 5% (w/v) aqueous sodium bicarbonate solution, dried (MgSO_4), filtered and evaporated to dryness to give 92 mg (0.23 mmol, 89%) as a pale yellow oil. nmr (CDCl_3)
8: 2.30 (6H, a methyl singlet and a methyl doublet),
10 2.33 (3H, s), 2.35-2.5 (6H, m), 2.75-2.85 (2H, m), 3.30 (H, d), 3.70 (3H, s), 4.37 (H, m), 6.83 (H, bs), 6.95-7.1 (4H, m). IR (neat) 3450, 1710 cm^{-1} .

Step G: Preparation of 7-(4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoic acid
15

Employing the procedure substantially as described in Example 1, Step E, the ester from Step G of this Example 2 is saponified to the subject 5-keto
20 acid.

Employing the procedure substantially as described in Example 2, Steps A through G, but substituting for the chloromethylbiphenyl employed in
Step A thereof, equimolar amounts of the chloromethyl
25 compounds described in Table II, there are produced the 5-keto esters, salts and acids also described in Table II in accordance with the following reaction sequence:

- 27 -

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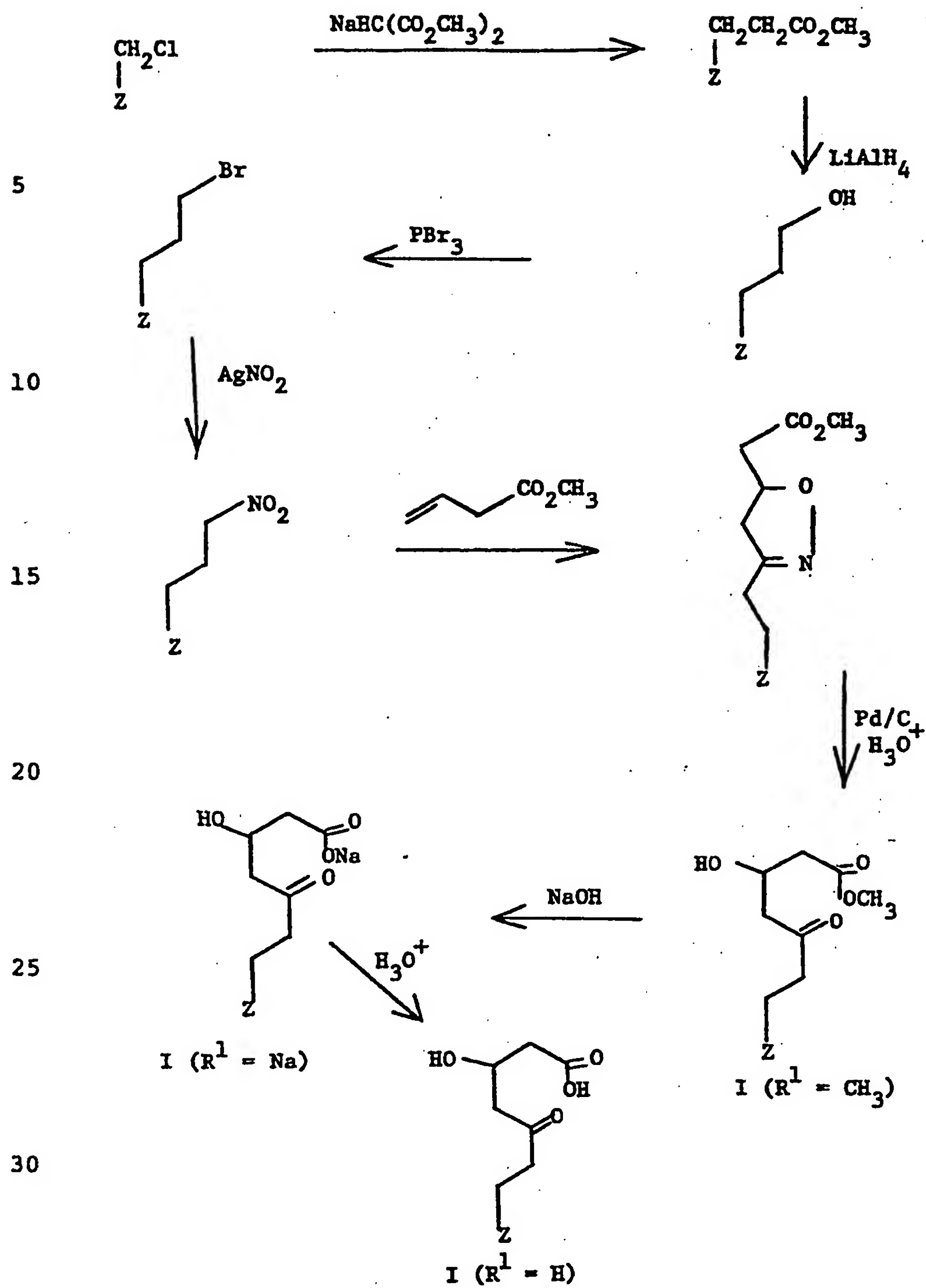
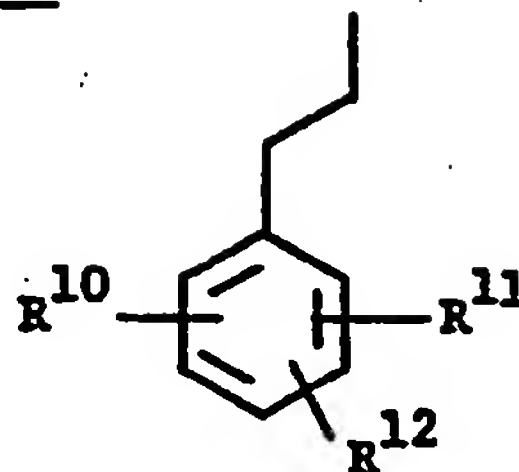


TABLE II

5

$$\begin{array}{c} | \\ E \\ | \\ Z \end{array}$$

=



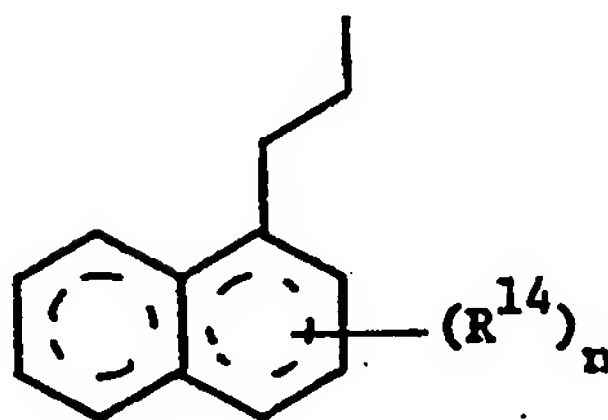
10

	R^{10}	R^{11}	R^{12}
	6-(4-fluorophenyl)-	2-chloro	4-chloro
	6-(4-chlorophenyl)-	2-chloro	4-chloro
15	6-(3,4-dichlorophenyl)-	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	4-methyl
	6-(3,4-dimethylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
20	6-(4-fluorophenyl)-	2-methyl	4-methyl
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
	6-(4-fluorobenzyloxy)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-methyl

25

$$\begin{array}{c} | \\ E \\ | \\ Z \end{array}$$

=



30

5	<u>n</u>	<u>R¹⁴</u>	
	1	2-methyl	naphthyl
	0	-	naphthyl
	2	2,6-dimethyl	naphthyl
	1	2-methyl	5,6,7,8-tetra- hydronaphthyl

EXAMPLE 310 7-(2,4-Dichlorophenyl)-3-hydroxy-5-oxoheptanoic acidStep A: Preparation of Methyl 7-(2,4-Dichlorophenyl)-3-hydroxy-5-oxo-6-heptenoate

Activated manganese dioxide (40 g) was added to a solution of methyl 7-(2,4-dichlorophenyl)-3,5-dihydroxy-6-heptenoate (6.8 g, 21.3 mmol) in chloroform (600 mL) and the black suspension was vigorously stirred at ambient temperature for 20 hours. After filtration and evaporation of the solvent the residual amber oil (4.5 g, 1 major spot on TLC with R_f 0.61 on Whatman MK6F silica using CHCl_3 -MeOH; 19:1 as eluent) was chromatographed on a Still column to obtain the product (3.9 g, 58%) as a pale yellow oil which solidified on standing, m.p. 77-79°C; NMR (CDCl_3) δ : 2.57 (2H, d, $J=6\text{Hz}$, $-\text{CH}_2\text{CO}_2-$), 2.93 (2H, d, $J=6\text{Hz}$, $-\text{CH}_2-\text{CO}-$), 3.70 (3H, s, $-\text{CO}_2\text{CH}_3$), 4.4-4.8 (H, m, $-\text{CH}(\text{OH})-$), 6.67 (H, d, $J=16\text{ Hz}$, $=\text{CH}-\text{CO}$), 7.1-7.7 (3H, m. ArH), 7.93 (H, d, $J=16\text{ Hz}$, $=\text{CH}$).

Analysis for $\text{C}_{14}\text{H}_{14}\text{Cl}_2\text{O}_4$.

30 Calcd.: C, 53.02; H, 4.45.

Found: C, 53.25; H, 4.50.

Step B: Preparation of Methyl 7-(2,4-Dichlorophenyl)-3-hydroxy-5-oxoheptanoate

Tributyltin hydride (450 μ L, 1.7 mmol) was added dropwise over 1-1/2 hours to a stirred solution of the ene-one ester from Step A (320 mg, 1 mmol) and tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) in dry THF (5 mL) at ambient temperature under N_2 . After standing at 20°C overnight the light-brown solution was distributed between water (100 mL) and ether (150 mL). The organic layer was separated and washed with water (2 x 100 mL), dried and evaporated. The residual oil (1 major spot on TLC with R_f 0.39 vis-a-vis 0.35 for the starting ene-one ester on Whatman MK6F silica using $CHCl_3$ -MeOH; 99:1 as eluent) was chromatographed on a Still column to obtain the product (260 mg, 81%) as a pale amber gum; NMR ($CDCl_3$) δ : 2.5-2.525 (2H, m, $-CH_2CO_2-$), 2.57-2.73 (2H, m, $-COCH_2C(OH)-$), 2.77 (2H, t, $J=7.5$ Hz, $Ar-CH_2CH_2CO-$), 2.98 (2H, t, $J=7.5$ Hz, $Ar-CH_2CH_2CO-$), 3.71 (3H, s, $-CO_2CH_3$), 4.45-4.51 (H, m, $-CH(OH)-$).
Analysis for $C_{14}H_{16}Cl_2O_4$
Calcd.: C, 52.68, H, 5.05.
Found: C, 52.47; H, 5.20.

25

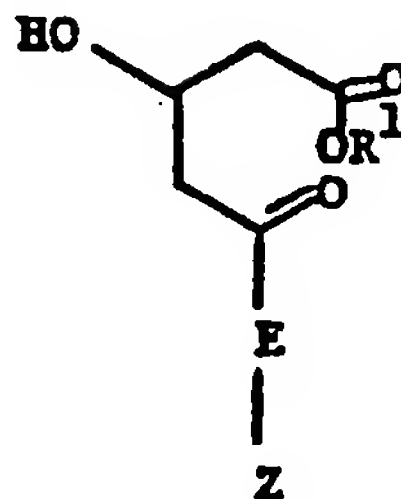
Step C: Preparation of 7-(2,4-dichlorophenyl)-3-hydroxy-5-oxoheptanoic acid

Employing the procedure substantially as described in Example 1, Step E, the ester from Step B of this Example 3 is saponified to the subject 5-oxo acid.

30

WHAT IS CLAIMED IS

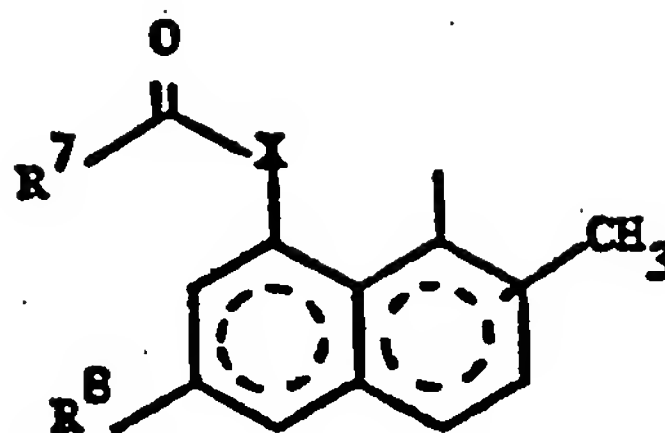
1. A compound of structural formula:



wherein:

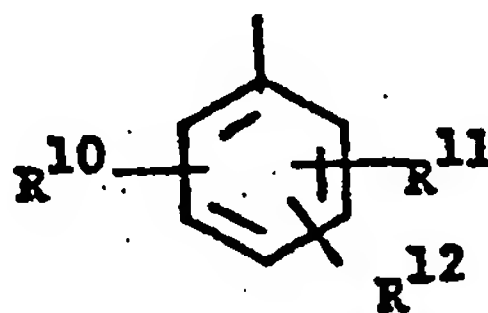
- 20 R^1 is
- 1) hydrogen,
 - 2) C_{1-4} alkyl,
 - 3) 2,3-dihydroxypropyl,
 - 4) alkali metal cation, or
- 25 5) ammonium of formula $NR^3R^4R^5R^6$
 wherein R^3 , R^4 , R^5 and R^6 are
 independently hydrogen or C_{1-4} alkyl or
 two of R^3 , R^4 , R^5 and R^6 are
 joined together to form a 5- or
 30 6-membered heterocycle with the nitrogen
 to which they are attached;
- E is $-CH_2CH_2-$, $-CH=CH-$, or $-(CH_2)_3-$; and

z. is 1)



wherein X is -O- or -NR⁹ wherein R⁹ is hydrogen or C₁₋₃alkyl;
R⁷ is C₂₋₈alkyl; and
R⁸ is hydrogen or -CH₃;

2)



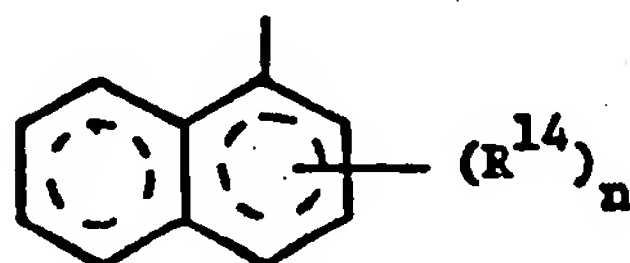
wherein R¹⁰, R¹¹ and R¹² are independently

- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C₁₋₄alkyl,
- d) halo-C₁₋₄alkyl,
- e) phenyl either unsubstituted or substituted with one or more of

- i) C₁₋₄alkoxy,
- ii) C₁₋₄alkyl,
- iii) C₂₋₈alkanoyloxy,
- iv) halo-C₁₋₄alkyl, or
- v) halo,
- f) OR¹³ wherein R¹³ is
 - i) hydrogen,
 - ii) C₂₋₈alkanoyl,
 - iii) benzoyl,

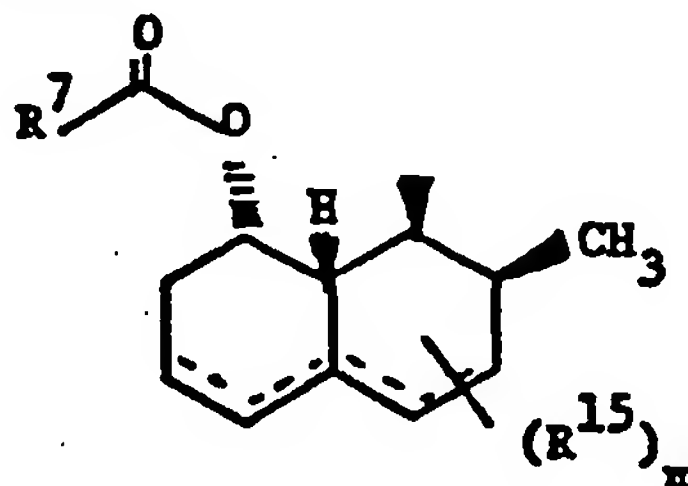
- iv) phenyl,
 v) halophenyl,
 vi) phenyl- C_{1-3} alkyl, either
 unsubstituted or substituted with
 one or more of halogen,
 C_{1-4} alkoxy, C_{1-4} alkyl or
 halo- C_{1-4} alkyl,
 vii) C_{1-9} alkyl,
 viii) cinnamyl,
 ix) halo- C_{1-4} alkyl,
 x) allyl,
 xi) C_{3-6} cycloalkyl- C_{1-3} alkyl, or
 xii) adamantyl- C_{1-3} alkyl;

3)



wherein n is 0-2 and R^{14} is halo or
 C_{1-4} alkyl; and

4)



wherein the dotted lines represent
 possible double bonds there being 0, 1 or
 2 double bonds;

m represents 1, 2 or 3; and

R^{15} is 1) methyl,
2) hydroxy,
3) C_{1-4} alkoxy,
4) oxo, or
5) halo.

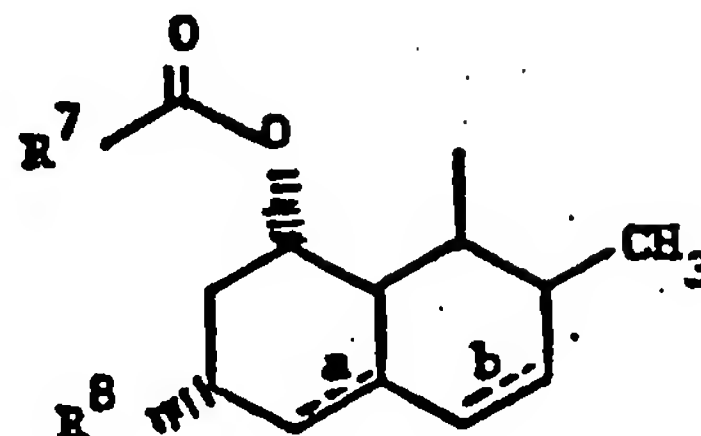
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2. The compound of Claim 1 wherein:
 R^1 is hydrogen, an alkali metal cation or an
ammonium cation;

10 E is $-CH=CH-$ or $-CH_2CH_2-$; and

Z is 1)

15

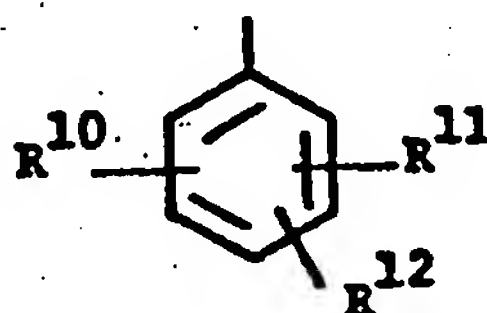


20

wherein R^{7a} is 2(S)-methylbutyryl or
2,2-dimethylbutyryl;

25

2)



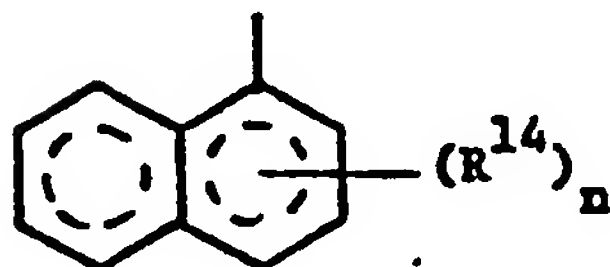
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wherein R^{10} , R^{11} and R^{12} are
independently

- a) halogen,
- b) C_{1-4} alkyl,
- c) halo- C_{1-4} alkyl,

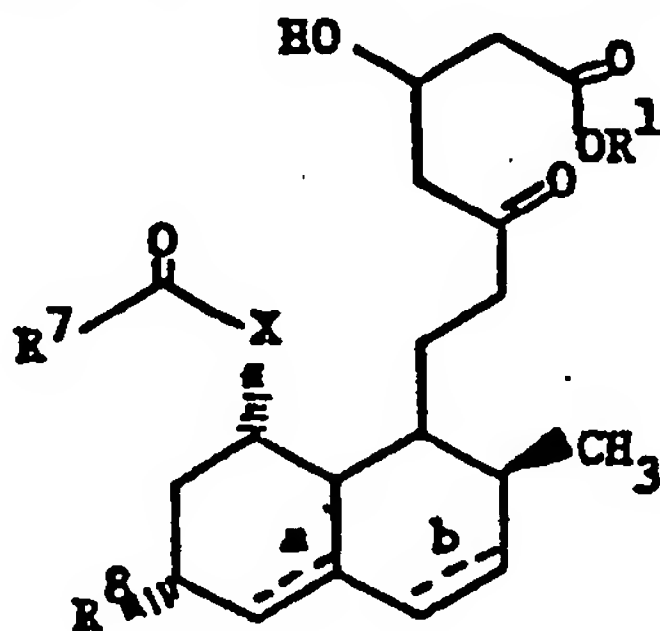
- d) phenyl with 1 to 3 substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy,
- e) OR^{13} , wherein R^{13} is
- i) phenyl,
 - ii) halophenyl, or
 - iii) phenyl substituted with 1-3 substituents selected from halogen and C_{1-4} alkyl,
 - iv) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy, C_{1-4} alkyl or halo- C_{1-4} alkyl; or

3)



wherein n is 0, 1 or 2, and R^{14} is methyl, and the ring system is naphthyl, or 5,6,7,8-tetrahydronaphthyl.

3. The compound of Claim 2 selected from:



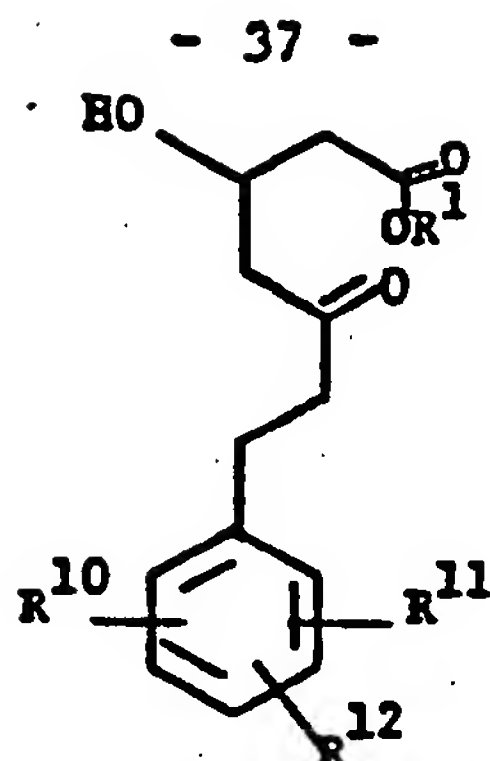
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	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^7 \text{C}- \end{array}$	R^8	X	a*	b
5	2(S)-methylbutyryl	-CH ₃	O	single	double
	2(S)-methylbutyryl	-CH ₃	O	single	single
	2(R)-methylbutyryl	-CH ₃	O	double	double
	2,2-dimethylbutyryl	-CH ₃	O	double	double
	2,2-dimethylbutyryl	-CH ₃	O	single	double
	2,2-dimethylbutyryl	-CH ₃	O	single	single
10	acetyl	-CH ₃	O	double	double
	2(S)-methylbutyryl	H	O	double	double
	2(S)-methylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	H	O	double	double
	2,2-dimethylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	-CH ₃	NH	single	single
15	2-methyl-2-ethyl- butyryl	-CH ₃	NH	single	single
	2-methylbutyryl	-CH ₃	NH	single	single
	4-fluorobenzoyl	-CH ₃	NH	single	single
	4-fluorophenyl- acetyl	-CH ₃	NH	single	single
	4- <u>tert</u> -butylbenzoyl	-CH ₃	NH	single	single
	acetyl	-CH ₃	NH	double	double
20	acetyl	-CH ₃	NCH ₃	single	single
	2,2-dimethylbutyryl	-CH ₃	NCH ₃	single	single
	2,2-dimethylbutyryl	-CH ₃	NH	double	double
25	2,2-dimethylbutyryl	-CH ₃	NH	double	double

* When a=single bond, the rings are trans-fused.

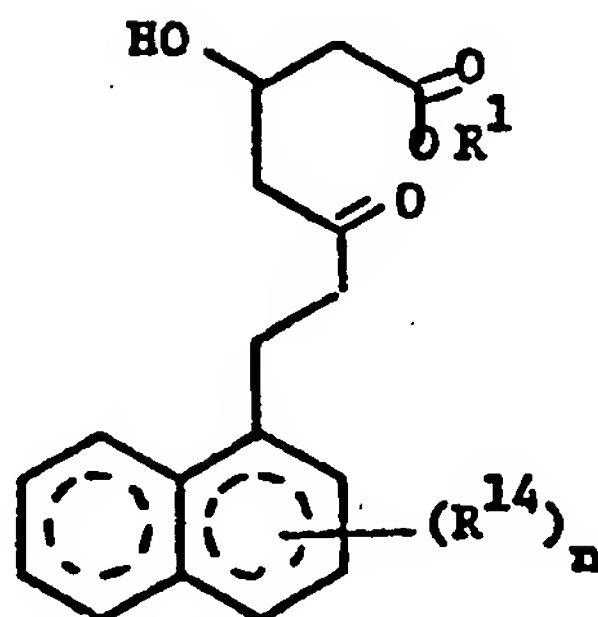
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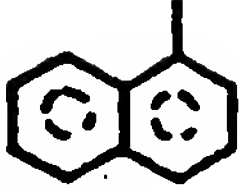
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	R ¹⁰	R ¹¹	R ¹²
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
	6-(4-fluorophenyl)-	2-chloro	4-chloro
	6-(4-chlorophenyl)-	2-chloro	4-chloro
15	6-(3,4-dichlorophenyl)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)	2-methyl	4-methyl
	6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
20	6-(4-fluorophenyl)	2-methyl	4-methyl
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
	6-(4-fluorobenzyloxy)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-methyl

25



30

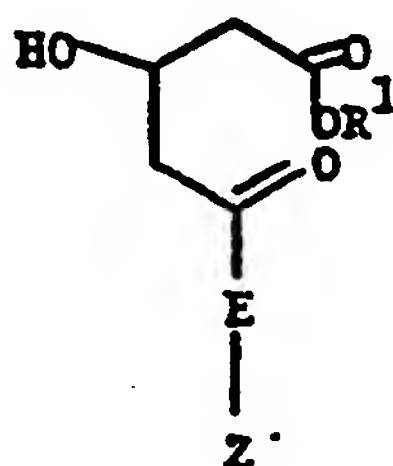
<u>n</u>		<u>R¹⁴</u>	
5	1	2-methyl	naphthyl
	0	-	naphthyl
	2	2,6-dimethyl	naphthyl
	1	2-methyl	5,6,7,8-tetra- hydronaphthyl

4. An antihypercholesterolemic pharmaceutical composition comprising a pharmaceutical carrier and an effective antihypercholesterolemic amount of a compound as claimed in Claim 1.

5. The formulation of Claim 4 wherein the antihypercholesterolemic compound is as claimed in Claim 2.

6. The formulation of Claim 5 wherein the antihypercholesterolemic compound is as claimed in Claim 3.

7. A process for the preparation of a compound of structural formula:



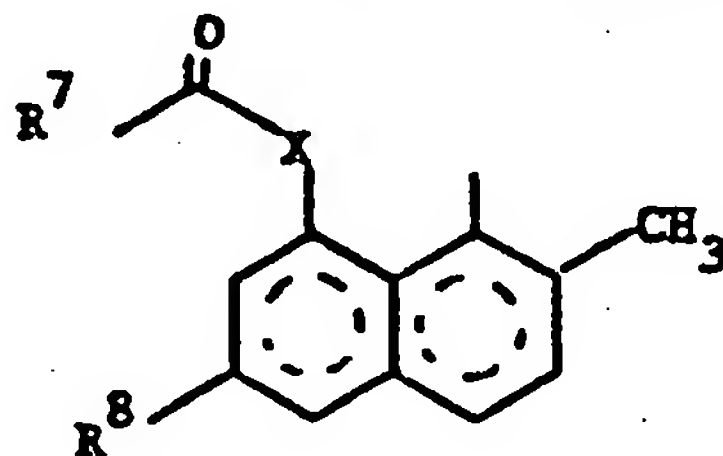
wherein:

R¹ is 1) hydrogen,
2) C₁₋₄alkyl,
3) 2,3-dihydroxypropyl,
4) alkali metal cation, or

5) ammonium of formula $\text{NR}^3\text{R}^4\text{R}^5\text{R}^6$
wherein R³, R⁴, R⁵ and R⁶ are
independently hydrogen or C₁₋₄alkyl or
two of R³, R⁴, R⁵ and R⁶ are
joined together to form a 5- or
6-membered heterocycle with the nitrogen
to which they are attached;

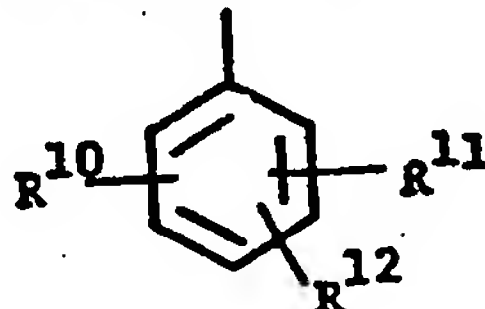
E is -CH₂CH₂-, -CH=CH-, or -(CH₂)₃-; and

Z is 1)



wherein X is -O- or NR^9 wherein R^9 is hydrogen or C_{1-3} alkyl;
 R^7 is C_{2-8} alkyl; and
 R^8 is hydrogen or $-\text{CH}_3$;

2)

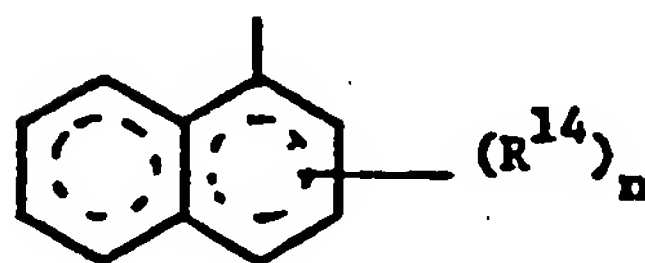


wherein R^{10} , R^{11} and R^{12} are independently

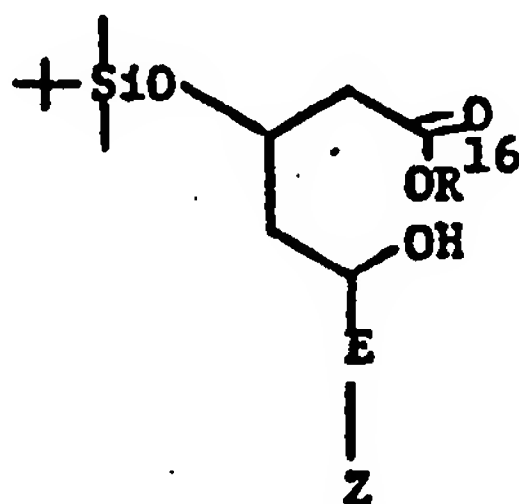
- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C_{1-4} alkyl,
- d) halo- C_{1-4} alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C_{1-4} alkoxy,
 - ii) C_{1-4} alkyl,
 - iii) C_{2-8} alkanoyloxy, or
 - iv) halo- C_{1-4} alkyl,
 - v) halo,
- f) OR^{13} wherein R^{13} is
 - i) hydrogen,
 - ii) C_{2-8} alkanoyl,
 - iii) benzoyl,
 - iv) phenyl,
 - v) halophenyl,
 - vi) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen,

- C_{1-4} alkoxy, C_{1-4} alkyl or
 halo- C_{1-4} alkyl,
 vii) C_{1-9} alkyl,
 viii) cinnamyl,
 5 ix) halo- C_{1-4} alkyl,
 x) allyl,
 xi) C_{3-6} cycloalkyl- C_{1-3} alkyl, or
 xii) adamantyl- C_{1-3} alkyl;

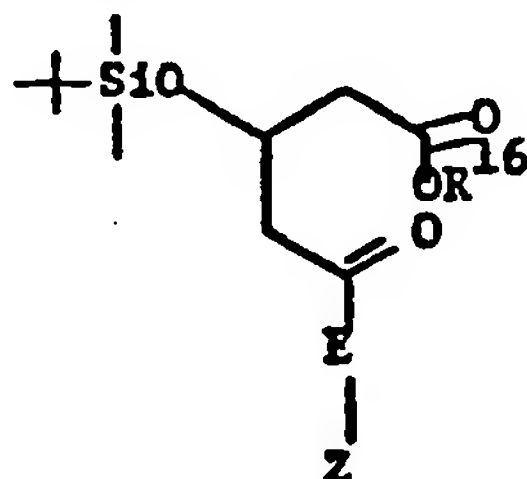
3)



15 wherein n is 0-2 and R^{14} is halo or
 C_{1-4} alkyl, which comprises treating a
 compound of structural formula:



25 wherein R^{16} is C_{1-4} alkyl, with an
 oxidizing agent to produce the compound
 of structural formula:

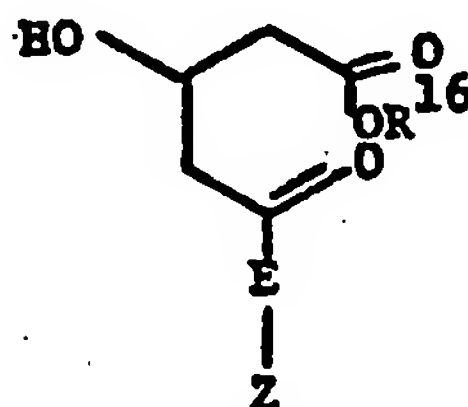


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-42-

followed by desilylation to produce the compound of structural formula:

5



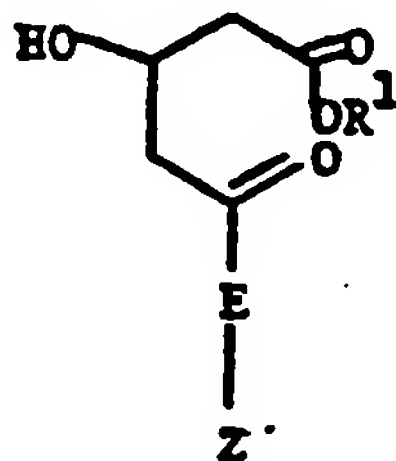
10

followed by treatment with alkali to produce the product wherein R¹⁶ is an alkali metal cation, followed by acidification to produce the compound wherein R¹⁶ is a hydrogen ion.

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CLAIMS FOR THE CONTRACTING STATE ATWHAT IS CLAIMED IS:

1. A process for the preparation of a compound of structural formula:



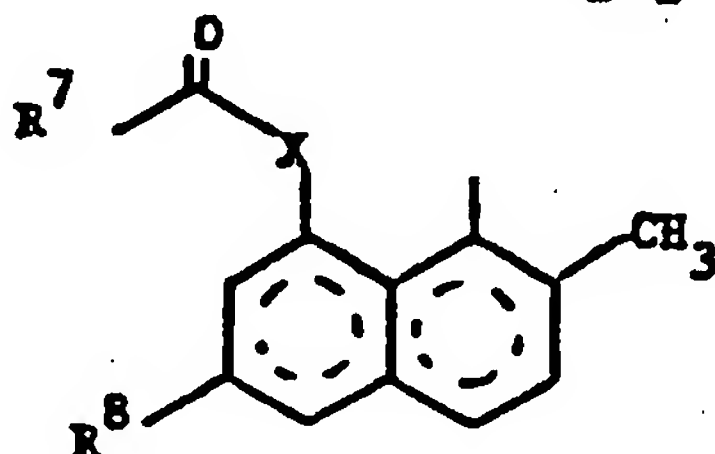
wherein:

R¹ is 1) hydrogen,
2) C₁₋₄alkyl,
3) 2,3-dihydroxypropyl,
4) alkali metal cation, or

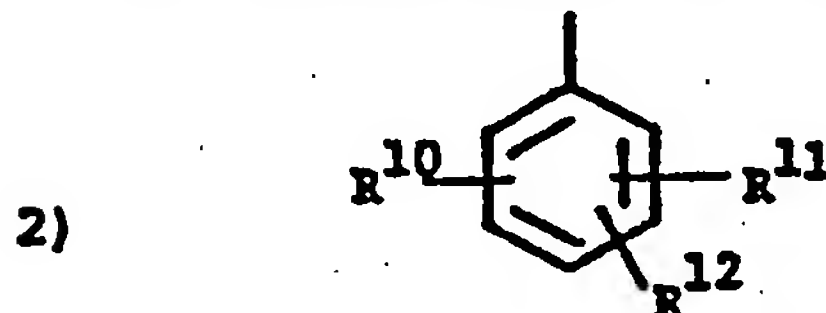
5) ammonium of formula $\text{NR}^3\text{R}^4\text{R}^5\text{R}^6$
wherein R³, R⁴, R⁵ and R⁶ are
independently hydrogen or C₁₋₄alkyl or
two of R³, R⁴, R⁵ and R⁶ are
joined together to form a 5- or
6-membered heterocycle with the nitrogen
to which they are attached;

E is -CH₂CH₂-, -CH=CH-, or -(CH₂)₃-; and

Z is 1)



wherein X is -O- or NR^9 wherein R^9 is hydrogen or C_{1-3} alkyl;
 R^7 is C_{2-8} alkyl; and
 R^8 is hydrogen or $-\text{CH}_3$;



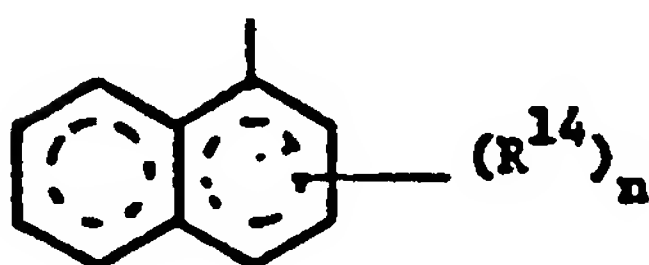
wherein R^{10} , R^{11} and R^{12} are independently

- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C_{1-4} alkyl,
- d) halo- C_{1-4} alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C_{1-4} alkoxy,
 - ii) C_{1-4} alkyl,
 - iii) C_{2-8} alkanoyloxy, or
 - iv) halo- C_{1-4} alkyl, ..
 - v) halo,
- f) OR^{13} wherein R^{13} is
 - i) hydrogen,
 - ii) C_{2-8} alkanoyl,
 - iii) benzoyl,
 - iv) phenyl,
 - v) halophenyl,
 - vi) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen,

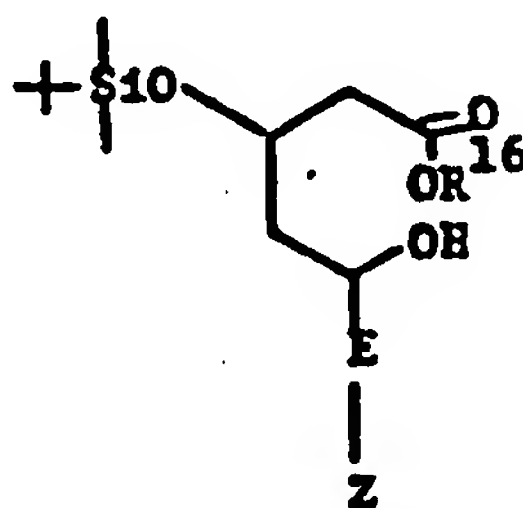
16991

- C_{1-4} alkoxy, C_{1-4} alkyl or
 halo- C_{1-4} alkyl,
 vii) C_{1-9} alkyl,
 viii) cinnamyl,
 5 ix) halo- C_{1-4} alkyl,
 x) allyl,
 xi) C_{3-6} cycloalkyl- C_{1-3} alkyl, or
 xii) adamantyl- C_{1-3} alkyl;

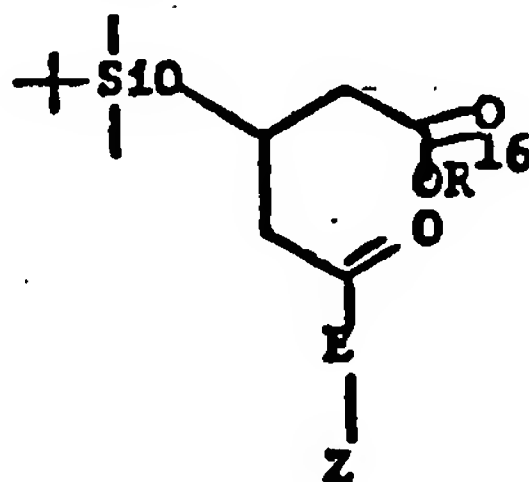
3)



15 wherein n is 0-2 and R^{14} is halo or
 C_{1-4} alkyl, which comprises treating a
 compound of structural formula:



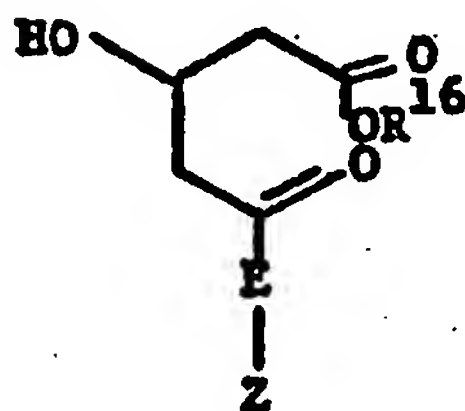
25 wherein R^{16} is C_{1-4} alkyl, with an
 oxidizing agent to produce the compound
 of structural formula:



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followed by desilylation to produce the compound of structural formula:



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followed by treatment with alkali to produce the product wherein R^{16} is an alkali metal cation, followed by acidification to produce the compound wherein R^{16} is a hydrogen ion.

15

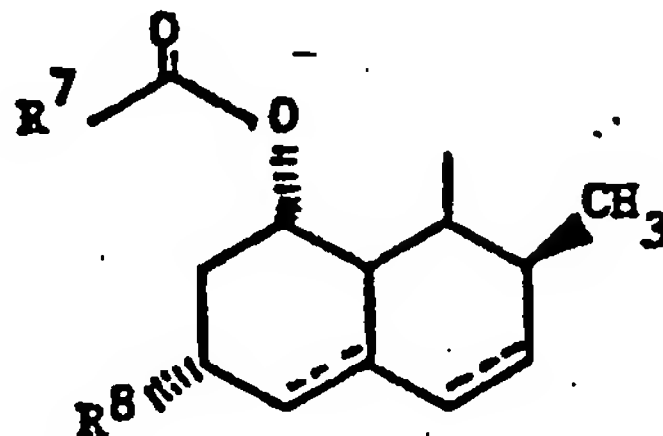
2. The process of Claim 1 wherein:

R^1 is hydrogen, an alkali metal cation or an ammonium cation;

E is $-CH=CH-$ or $-CH_2CH_2-$; and

20

Z is 1)

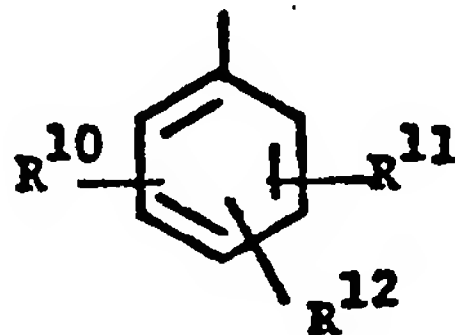


25

wherein R^7 is 2(S)-methylbutyryl or 2,2-dimethylbutyryl;

30

2)



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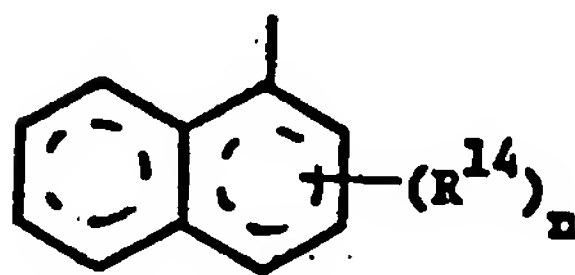
wherein R^{10} , R^{11} and R^{12} are independently

- a) halogen,
- b) C_{1-4} alkyl,
- c) halo- C_{1-4} alkyl,
- d) phenyl with 1 to 3 substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy,

e) OR^{13} , wherein R^{13} is

- i) phenyl,
- ii) halophenyl, or
- iii) phenyl substituted with 1-3 substituents selected from halogen and C_{1-4} alkyl; or
- iv) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy, C_{1-4} alkyl, or halo- C_{1-4} alkyl; or

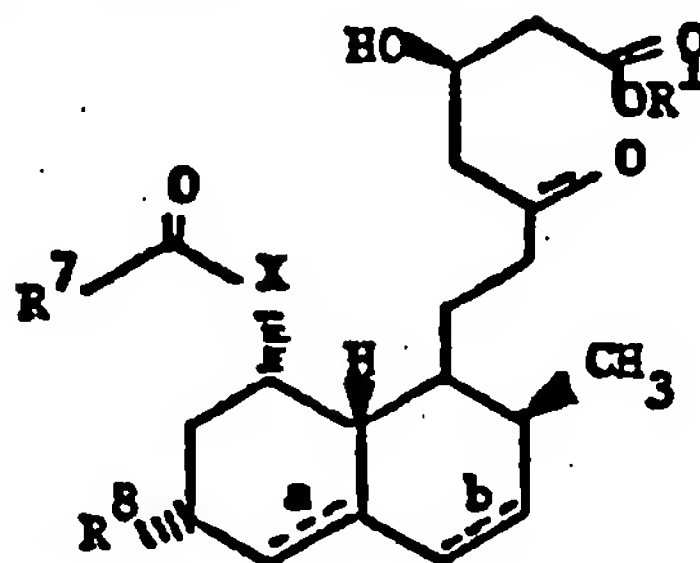
3)



wherein n is 0, 1 or 2, and R^{14} is methyl and the ring system is naphthalene or 5,6,7,8-tetrahydronaphthalene.

3. The process of Claim 2 for the preparation of a compound selected from:

5

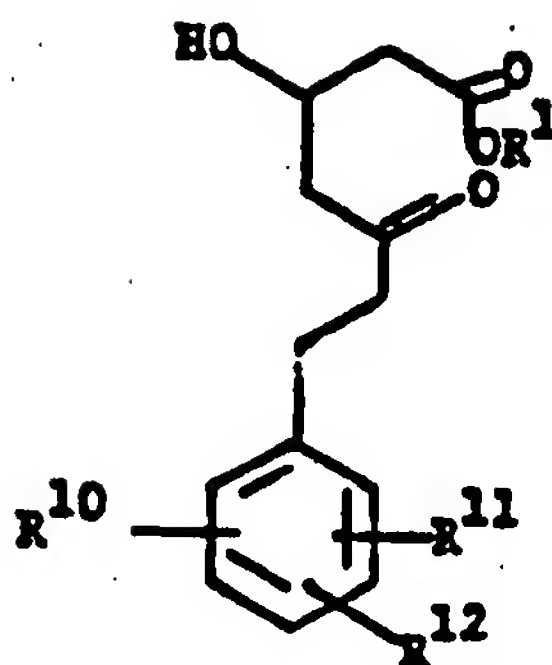


10	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^7\text{C}- \end{array}$	R^8	X	a*	b
	2(S)-methylbutyryl	$-\text{CH}_3$	O	single	double
	2(S)-methylbutyryl	$-\text{CH}_3$	O	single	single
	2(R)-methylbutyryl	$-\text{CH}_3$	O	double	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	O	double	double
15	2,2-dimethylbutyryl	$-\text{CH}_3$	O	single	double
	2,2-dimethylbutyryl	$-\text{CH}_3$	O	single	single
	acetyl	$-\text{CH}_3$	O	double	double
	2(S)-methylbutyryl	H	O	double	double
	2(S)-methylbutyryl	H	O	single	single
20	2,2-dimethylbutyryl	H	O	double	double
	2,2-dimethylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	$-\text{CH}_3$	NH	single	single
	2-methyl-2-ethylbutyryl	$-\text{CH}_3$	NH	single	single
25	2-methylbutyryl	$-\text{CH}_3$	NH	single	single
	4-fluorobenzoyl	$-\text{CH}_3$	NH	single	single
	4-fluorophenylacetyl	$-\text{CH}_3$	NH	single	single
	4-tert-butylbenzoyl	$-\text{CH}_3$	NH	single	single
30	acetyl	$-\text{CH}_3$	NH	double	double
	acetyl	$-\text{CH}_3$	NCH_3	single	single
	2,2-dimethylbutyryl	$-\text{CH}_3$	NCH_3	single	single
	2,2-dimethylbutyryl	$-\text{CH}_3$	NH	double	double

* When a=single bond, the rings are trans-fused.

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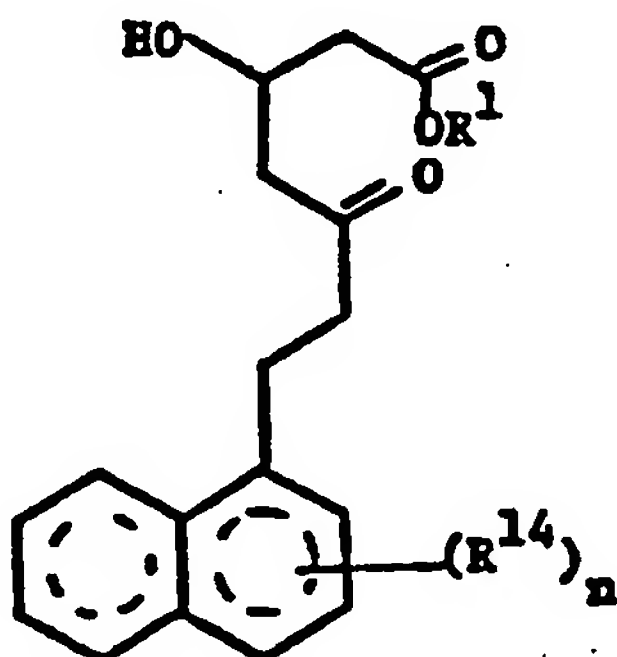
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10

	R ¹⁰	R ¹¹	R ¹²
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
	6-(4-fluorophenyl)-	2-chloro	4-chloro
	6-(4-chlorophenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)	2-chloro	4-chloro
15	6-(4-fluoro-3-methylphenyl)	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)	2-methyl	4-methyl
	6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
	6-(4-fluorophenyl)	2-methyl	4-methyl
20	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
	6-(4-fluorobenzyloxy)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)	2-chloro	4-methyl

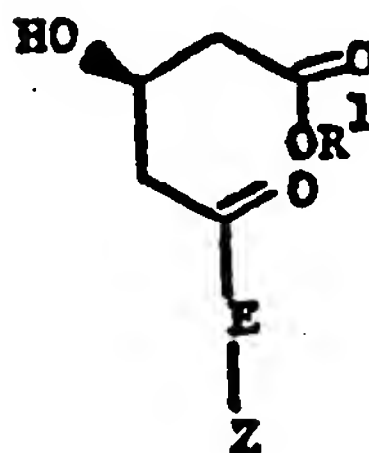
25



30

<u>n</u>		<u>R¹⁴</u>	
5	1	2-methyl	naphthyl
	0	-	naphthyl
	2	2,6-dimethyl	naphthyl
	1	2-methyl	5,6,7,8-tetrahydronaphthyl

10 4. A process for the preparation of a compound of formula



15

wherein

20 R¹ is

- 1) hydrogen,
- 2) C₁₋₄alkyl,
- 3) 2,3-dihydroxypropyl,
- 4) alkali metal cation, or

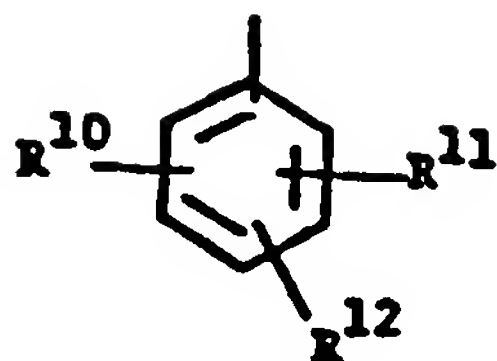
25 5) ammonium of formula $\text{NR}^3\text{R}^4\text{R}^5\text{R}^6$ ⁺ wherein R³, R⁴, R⁵ and R⁶ are independently hydrogen or C₁₋₄alkyl or two of R³, R⁴, R⁵ and R⁶ are jointed together to form a 5- or

30 6-membered heterocycle with the nitrogen to which they are attached;

E is -CH₂CH₂-, or -(CH₂)₃-; and

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Z. is 1)

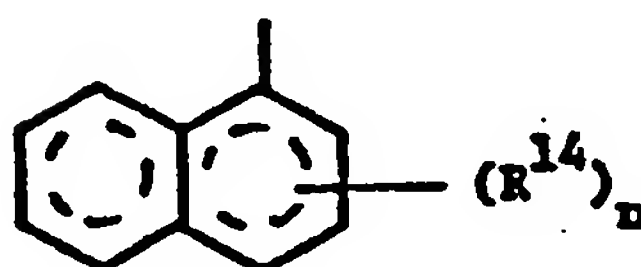


wherein R¹⁰, R¹¹ and R¹² are independently

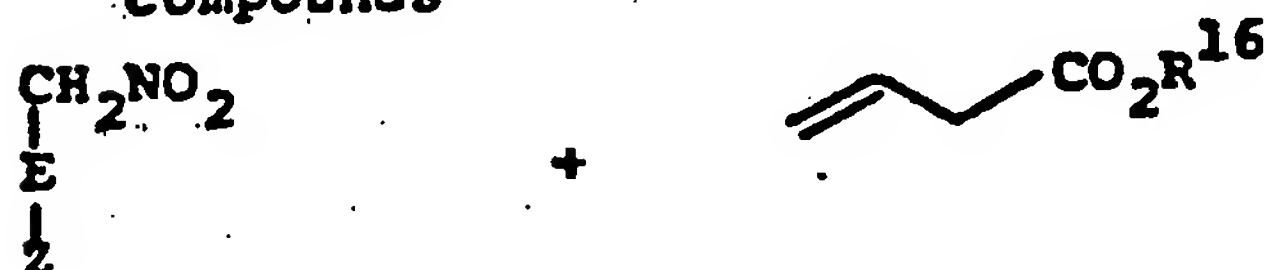
- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C₁₋₄alkyl,
- d) halo-C₁₋₄alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C₁₋₄alkoxy,
 - ii) C₁₋₄alkyl,
 - iii) C₂₋₈alkanoyloxy,
 - iv) halo-C₁₋₄alkyl, or
 - v) halo,
- f) OR¹³ wherein R¹³ is
 - i) hydrogen,
 - ii) C₂₋₈alkanoyl,
 - iii) benzoyl,
 - iv) phenyl,
 - v) halophenyl,
 - vi) phenyl-C₁₋₃alkyl, either unsubstituted or substituted with one or more of halogen, C₁₋₄alkoxy, C₁₋₄alkyl or halo-C₁₋₄alkyl,
 - vii) C₁₋₉alkyl,
 - viii) cinnamyl,

- ix) halo-C₁₋₄alkyl,
- x) allyl,
- xi) C₃₋₆cycloalkyl-C₁₋₃alkyl, or
- xii) adamantyl-C₁₋₃alkyl;

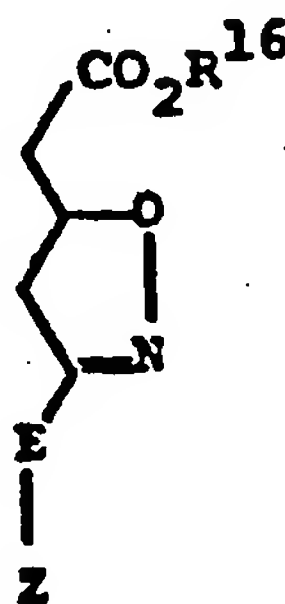
2)



wherein n is 0-2, and R^{14} is halo, or C₁₋₄ alkyl which comprises reacting the compounds



to produce the compound of structural formula:

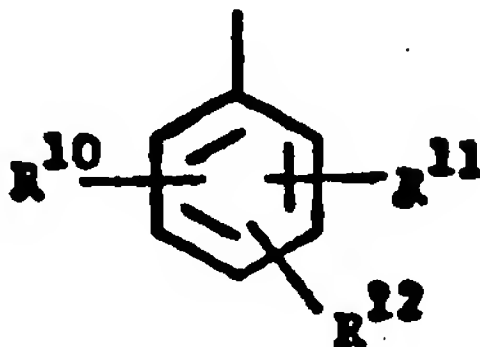


followed by catalytic reduction to produce the desired compound wherein R^1 is R^{16} ; followed by treatment with alkali to produce the product wherein R^1 is an alkali metal cation, followed by acidification to produce the compound wherein R^1 is a hydrogen ion.

5. The process of Claim 4 wherein:
 R^i is hydrogen, an alkali metal cation or an ammonium cation;

E is $-CH_2CH_2-$; and

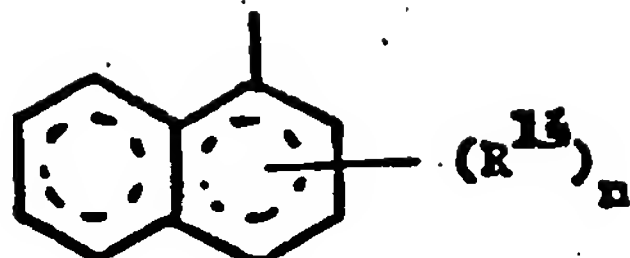
Z is 1)



wherein R^{10} , R^{11} and R^{12} are independently

- a) halogen,
- b) C_{1-4} alkyl,
- c) halo- C_{1-4} alkyl,
- d) phenyl with 1 to 3 substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy,
- e) OR^{13} , wherein R^{13} is
 - i) phenyl,
 - ii) halophenyl, or
 - iii) phenyl substituted with 1-3 substituents selected from halogen and C_{1-4} alkyl; or
 - iv) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy, C_{1-4} alkyl, or halo- C_{1-4} alkyl; or

2)



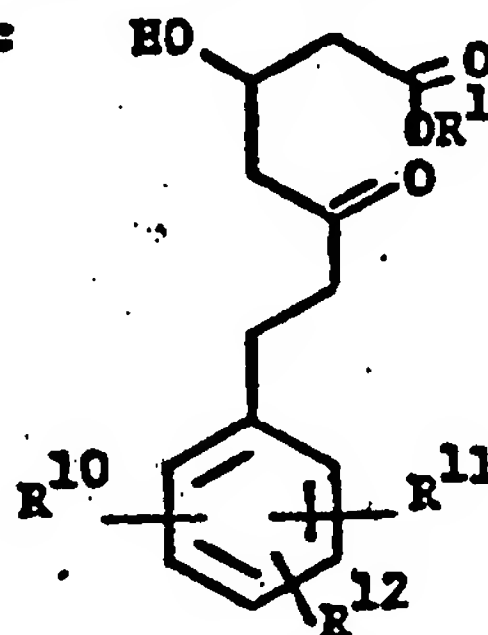
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10

wherein n is 0, 1 or 2, and R^{14} is methyl and the ring system is naphthalene or 5,6,7,8-tetrahydronaphthalene.

6. The process of Claim 5 for preparation of a compound selected from:

15



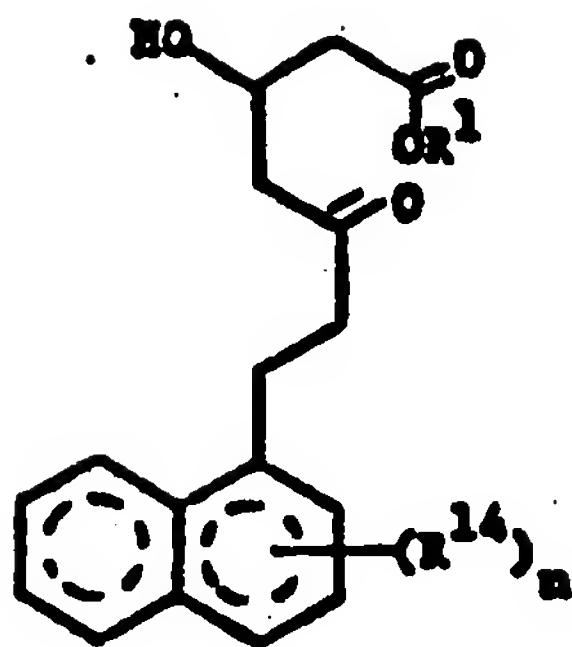
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R^{10}	R^{11}	R^{12}
6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
6-(4-fluorophenyl)-	2-chloro	4-chloro
6-(4-chlorophenyl)-	2-chloro	4-chloro
6-(3,4-dichlorophenyl)	2-chloro	4-chloro
6-(4-fluoro-3-methylphenyl)	2-chloro	4-chloro
6-(3,4-dichlorophenyl)	2-methyl	4-methyl
6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
6-(4-fluorophenyl)	2-methyl	4-methyl
6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
6-(4-fluorobenzoyloxy)	2-chloro	4-chloro
6-(4-fluoro-3-methylphenyl)-	2-chloro	4-methyl

and



10

n

1

0

2

1

R¹⁴

2-methyl

-

2,6-dimethyl

2-methyl

naphthyl

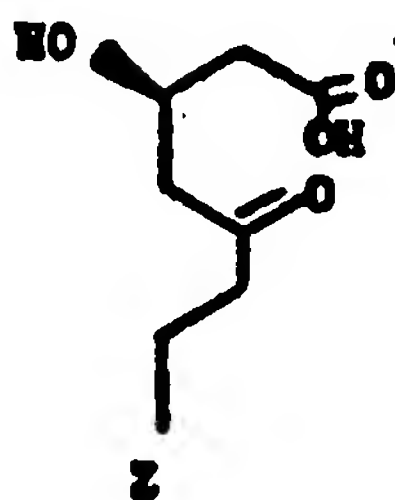
naphthyl

naphthyl

5,6,7,8-tetra-
hydronaphthyl

15

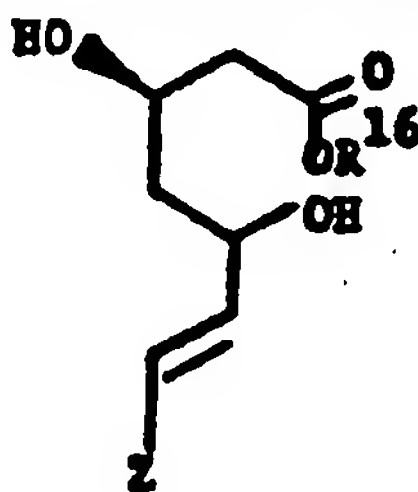
7. A process for the preparation of a compound of structural formula:



20

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wherein Z is as defined in Claim 1, which comprises treating a compound of structural formula:

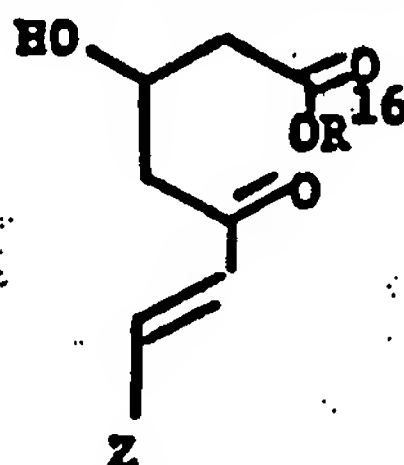


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with activated manganese dioxide to produce the compound of structural formula:



10 followed by treatment with tri-n-butyltin hydride and tetrakis (triphenylphosphine)palladium (0).

EUROPEAN PATENT APPLICATION

Application number: 84113599.9

Date of filing: 12.11.84

Int. Cl.⁴: **C 07 C 59/90, C 07 C 69/738, C 07 C 69/76, C 07 C 69/62, C 07 F 7/02, C 07 C 33/46, C 07 C 25/22, C 07 D 261/04 // A61K31/19**

Priority: 14.11.83 US 550707

Date of publication of application: 22.05.85
Bulletin 85/21

Designated Contracting States: AT BE CH DE FR GB IT
LI LU NL SE

Date of deferred publication of search
report: 07.08.85 Bulletin 85/32

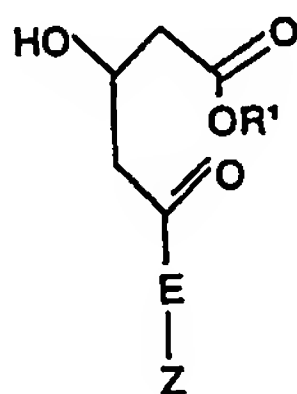
Applicant: **MERCK & CO. INC.**, 126, East Lincoln Avenue
P.O. Box 2000, Rahway New Jersey 07065 (US)

Inventor: **Hoffman, William F.**, 740 Wiekel Road,
Lansdale Pennsylvania 19446 (US)
Inventor: **Lee, Ta Jyh**, 1921 Supplee Road, Lansdale
Pennsylvania 19446 (US)
Inventor: **Stokker, Gerald E.**, Plymouth Road, Gwynedd
Valley Pennsylvania 19446 (US)

Representative: **Ablitz, Walter, Dr.-Ing. et al, Ablitz, Morf,**
Gritschneider, Freiherr von Wittgenstein
Postfach 86 01 09, D-8000 München 86 (DE)

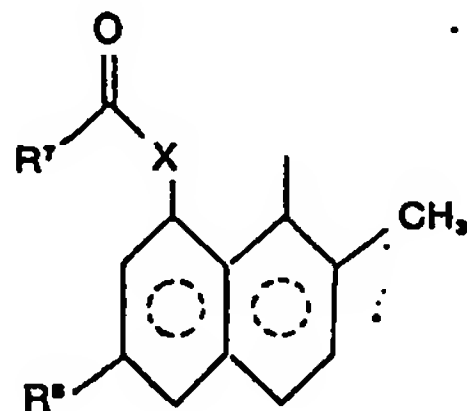
Oxo-analogs of mevinolin-like antihypercholesterolemic agents.

Mevinolin-like compounds of the structural formula:



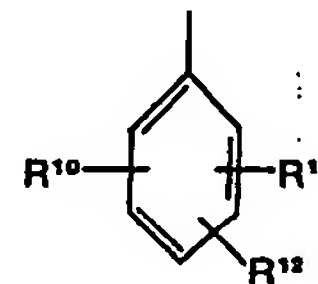
are disclosed wherein:

R¹ is, e.g., hydrogen or C₁₋₄alkyl;
E is -CH₂CH₂-, -CH=CH-, or -(CH₂)₃-; and
Z is 1)



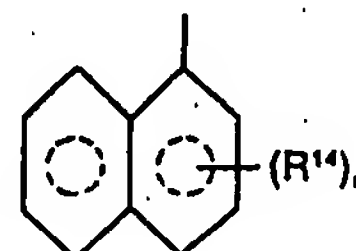
wherein X is -O- or -NR⁹ wherein R⁹ is hydrogen or C₁₋₃ alkyl;
R⁷ is C₂₋₄alkyl; and
R⁸ is hydrogen or -CH₃;

2)



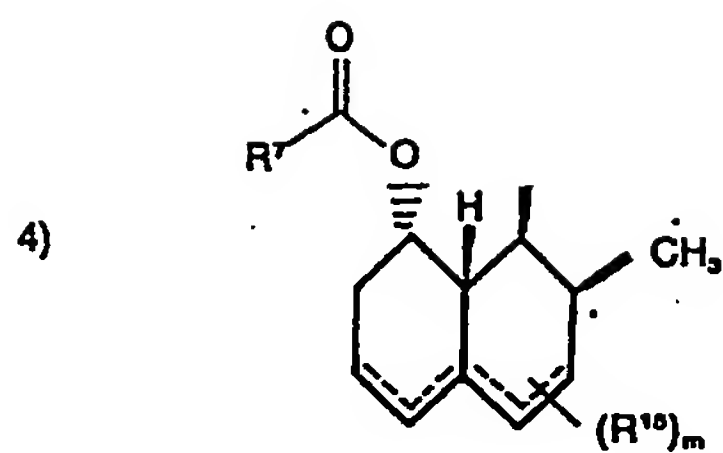
wherein R¹⁰, R¹¹ and R¹² are independently, e.g., hydrogen, halogen or C₁₋₄alkyl;

3)



wherein n is 0-2 and R¹⁴ is halo or C₁₋₄alkyl; or

(Continuation next page)



wherein the dotted lines represent possible double bonds there being 0, 1 or 2 double bonds;

m represents 1, 2 or 3; and

R^{10} is methyl, hydroxy, C_{1-4} alkoxy, oxo, or halo.

Those compounds are potent HMG-CoA reductase inhibitors possessing one less asymmetric center.



European Patent
Office

EUROPEAN SEARCH REPORT

0142146
Application Number

EP 84 11 3599

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	GB-A-1 555 831 (SANKYO) * Page 1, lines 28-31 *	1	C 07 C 59/90 C 07 C 69/738 C 07 C 69/76 C 07 C 69/62 C 07 F 7/02
A	GB-A-2 055 100 (SANKYO) * Claim 1 *	1	C 07 C 33/46 C 07 C 25/22 C 07 C 79/12
A	GB-A-2 073 199 (SANKYO) * Claim 1 *	1	C 07 D 261/04 // A 61 K 31/19
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			C 07 C 59/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE.		Date of completion of the search 04-04-1985	Examiner KLAG M. J.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

⑩



Europäisches Patentamt

European Patent Office

Office européen des brevets

⑪ Publication number:

**0 142 146
B1**

⑫

EUROPEAN PATENT SPECIFICATION

⑬ Date of publication of patent specification: 31.08.88

⑭ Application number: 84113599.9

⑮ Date of filing: 12.11.84

⑯ Int. Cl.⁴: C 07 C 59/90, C 07 C 69/738,
C 07 C 69/76, C 07 C 69/62,
C 07 F 7/02, C 07 C 33/46,
C 07 C 25/22, C 07 D 261/04 //
A61K31/19

⑰ Oxo-analogs of mevinolin-like antihypercholesterolemic agents.

⑱ Priority: 14.11.83 US 550707

⑲ Date of publication of application:
22.05.85 Bulletin 85/21

⑳ Publication of the grant of the patent:
31.08.88 Bulletin 88/35

㉑ Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

㉒ References cited:
EP-A-0 052 366
EP-A-0 068 038
GB-A-1 555 831
GB-A-2 055 100
GB-A-2 073 199

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EP 0 142 146 B1

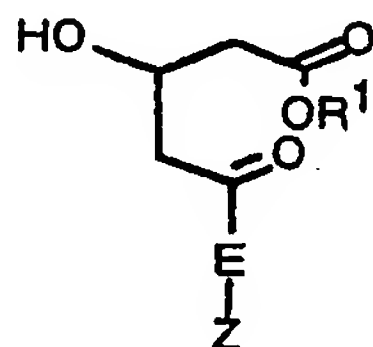
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Courier Press, Leamington Spa, England.

Description

Summary of the Invention

This invention is concerned with novel compounds of structural formula I:

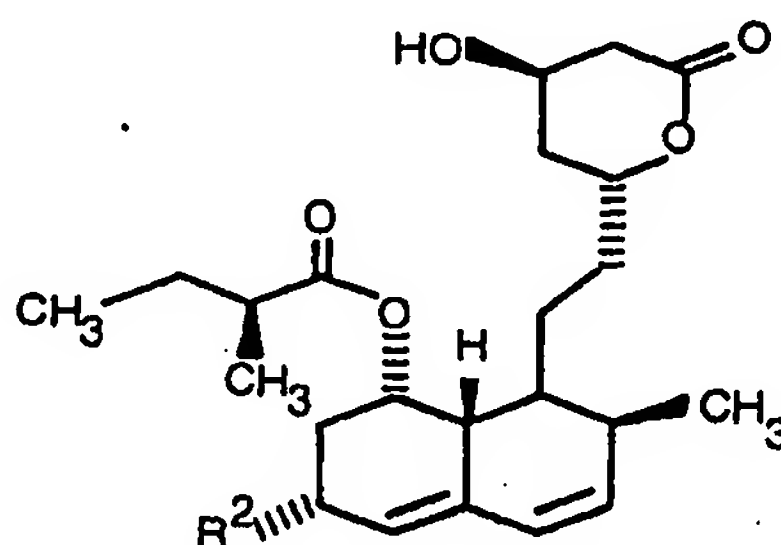


wherein Z is a variety of mono- and bi-carbocyclic moieties with various substituents well known to those skilled in the art of 3-hydroxy-3-methylglutaryl Coenzyme A (HMG—CoA) reductase inhibitors useful in the treatment of familial hypercholesterolemia, hyperlipemia and atherosclerosis.

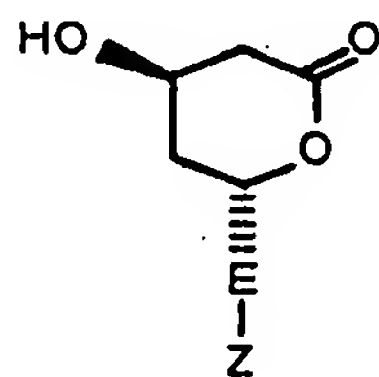
The invention is also concerned with novel processes for the preparation of the novel compounds; pharmaceutical formulations comprising a novel compound as active ingredient; and a method of treating familial hypercholesterolemia, hyperlipemia, and atherosclerosis.

Background of the Invention

Over the past several years a number of structurally related antihypercholesterolemic agents acting by inhibition of HMG—CoA reductase have been reported in the patent literature and elsewhere. The compounds have varied from the natural fermentation products, compactin and mevinolin,

Compactin ($R^2 = H$)Mevinolin ($R^2 = CH_3$)

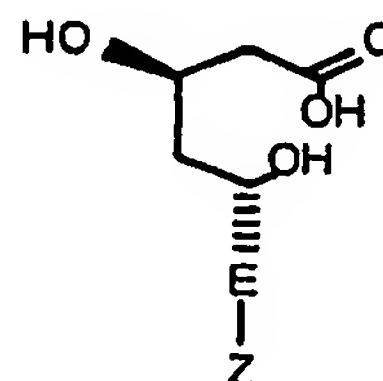
(see GB—A—1,555,831, GB—A—2,055,100 and GB—A—2,073,199) to di- and tetrahydro derivatives thereof (see EP—A—0,052,366); to analogs with different esters in the 8-position of the polyhydronaphthalene moiety, to totally synthetic analogs, wherein the polyhydronaphthalene moiety is replaced by substituted mono- and bicyclic aromatics, and biphenyls (see EP—A—0,068,038). But in all instances the active compound included a 4-hydroxytetrahydropyran-2-one ring or the corresponding 3,5-dihydroxy acid, or derivatives thereof, formed by opening the pyranone ring such as:



II

4-hydroxytetrahydropyran-2-one

or



IIa

3,5-dihydroxy-acid

In all of these compounds the 3,5-dihydroxy acid or corresponding lactone moiety is present and the particular stereochemistry depicted is essential for manifestation of the optimum enzyme inhibitory activity.

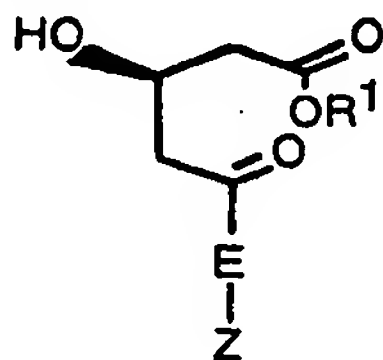
Now with the present invention there are provided compounds structurally related to those lactones

and dihydroxy acids that do not have the 5-hydroxy functionality, do not form a lactone ring, and are incapable of stereochemical variation at the 5-position of the acid because the 5-carbon is not asymmetric. On the contrary, the 5-carbon carries an oxo function which greatly facilitates the total synthesis of active compounds in that by eliminating one asymmetric center it is unnecessary to separate diastereoisomers or to conduct a stereoselective synthesis to obtain optimum enzyme inhibitory activity. It is believed that structures I are reduced *in situ* to generate the "active" inhibitors of structure II or IIa.

The active compounds of this invention are useful in either the racemic form or as the 3(R)-isomer. Those compounds produced by total synthesis are obtained initially as racemates, but may be resolved by standard methods into 3(R)- and 3(S)-isomers. Compounds of Structure I which are synthesized starting from natural fermentation products such as mevinolin and its analogs are obtained as the optically pure 3(R)-isomers.

Detailed Description of the Invention

The novel compounds of this invention have structural formula:



wherein

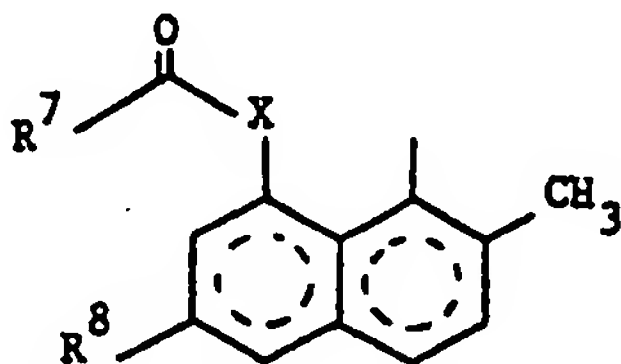
R¹ is

- 1) hydrogen,
- 2) C₁₋₄alkyl,
- 3) 2,3-dihydroxypropyl,
- 4) alkali metal cation, such as Na⁺, or K⁺, or
- 5) ammonium of formula N⁺R³R⁴R⁵R⁶

wherein R³, R⁴, R⁵ and R⁶ are independently hydrogen or C₁₋₄alkyl or two of R³, R⁴, R⁵ and R⁶ are joined together to form a 5 or 6-membered heterocycle such as pyrrolidino or piperidino with the nitrogen to which they are attached;

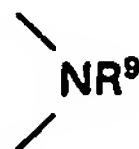
E is —CH₂CH₂—, —CH=CH—, or —(CH₂)₃—; and

Z is 1)



wherein the dotted lines represent all of the possible oxidation states of the bicyclic system such as naphthalene, dihydro-, tetrahydro-, hexahydro-, octahydro-, and decahydronaphthalene;

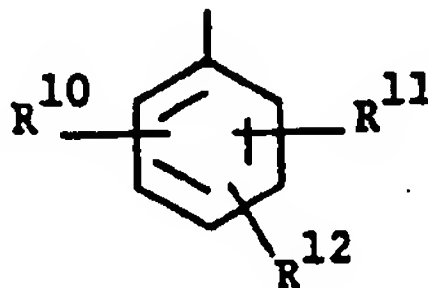
X is —O— or



wherein

- R⁹ is H or C₁₋₃alkyl;
R⁷ is C₂₋₈alkyl; and
R⁸ is H or —CH₃;

2)



wherein R¹⁰, R¹¹ and R¹² are independently

- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C₁₋₄alkyl,
- d) halo-C₁₋₄alkyl,

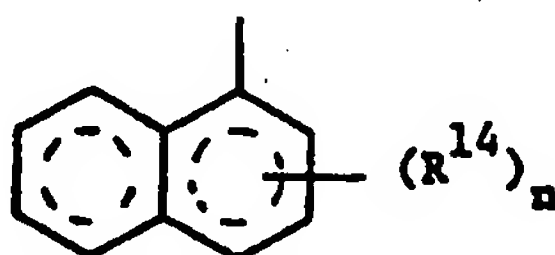
e) phenyl either unsubstituted or substituted with one or more of

- i) C₁₋₄alkoxy,
- ii) C₁₋₄alkyl,
- iii) C₂₋₈alkanoyloxy, or
- iv) halo-C₁₋₄alkyl,
- v) halo, such as bromo, chloro or fluoro,

f) OR¹³ wherein R¹³ is

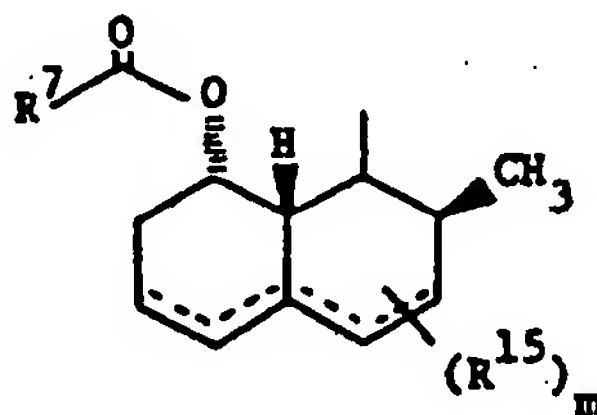
- i) hydrogen,
- ii) C₂₋₈alkanoyl,
- iii) benzoyl,
- iv) phenyl,
- v) halophenyl,
- vi) phenyl-C₁₋₃alkyl, either unsubstituted or substituted with one or more of halogen, C₁₋₄ alkoxy, C₁₋₄alkyl or halo-C₁₋₄alkyl,
- vii) C₁₋₈alkyl,
- viii) cinnamyl,
- ix) halo-C₁₋₄alkyl,
- x) allyl,
- xi) C₃₋₆cycloalkyl-C₁₋₃alkyl,
- xii) adamantyl-C₁₋₃alkyl,

3)



wherein n is 0—2, and R¹⁴ is halo such as chloro, bromo or fluoro, or C₁₋₄ alkyl, and

4)



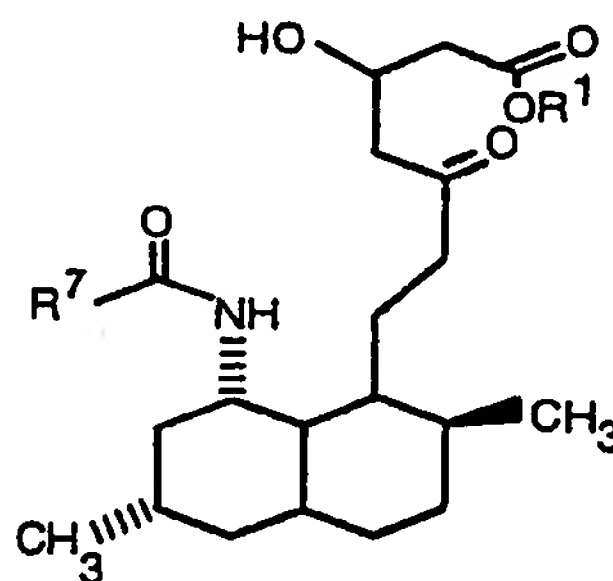
wherein the dotted lines represent possible double bonds there being 0, 1 or 2 double bonds;

m represents 1, 2 or 3; and

R¹⁵ is

- 1) methyl,
- 2) hydroxy,
- 3) C₁₋₄ alkoxy,
- 4) oxo or
- 5) halo;

or they have structural formula



wherein R¹ is hydrogen, an alkali metal cation or an ammonium cation and wherein R⁷ is 4-fluorobenzoyl, 4-tert-butylbenzoyl or 4-fluorophenylacetyl.

Preferred embodiments of the novel compounds are those in which:

R¹ is hydrogen, an alkali metal cation or an ammonium cation;

E is $-\text{CH}=\text{CH}-$ or $-\text{CH}_2\text{CH}_2-$; and
Z is

5

1)

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wherein

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is 2-methylbutyryl or 2,2-dimethylbutyryl;

20

2)

25

wherein R^{10} , R^{11} and R^{12} are independently

30

a) halogen,

b) C_{1-4} alkyl,

c) halo- C_{1-4} alkyl,

d) phenyl with 1 to 3 substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy,

e) OR^{13} , wherein R^{13} is

i) phenyl,

ii) halophenyl, or

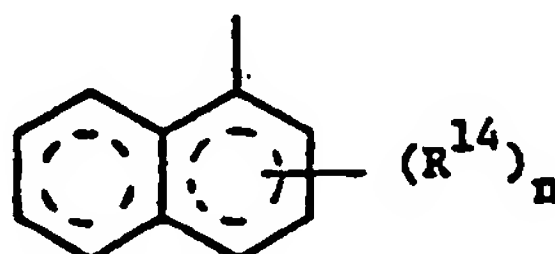
iii) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy,

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C_{1-4} alkyl or halo- C_{1-4} alkyl; or

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3)



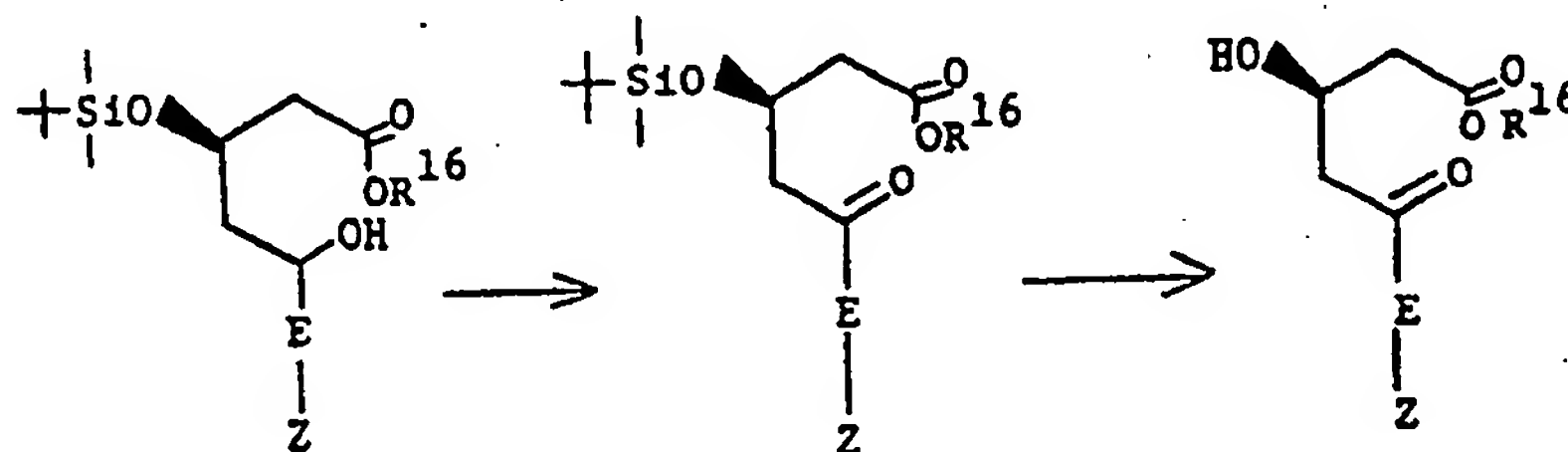
wherein n is 0, 1 or 2 and R^{14} is methyl and the ring system is naphthalene or 5,6,7,8-tetrahydronaphthalene.

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One novel process for preparing the novel compounds of this invention is particularly useful when starting with compounds with a pre-formed 4-hydroxytetrahydropyran-2-one moiety or the corresponding 3,5-dihydroxy acid and is illustrated as follows:

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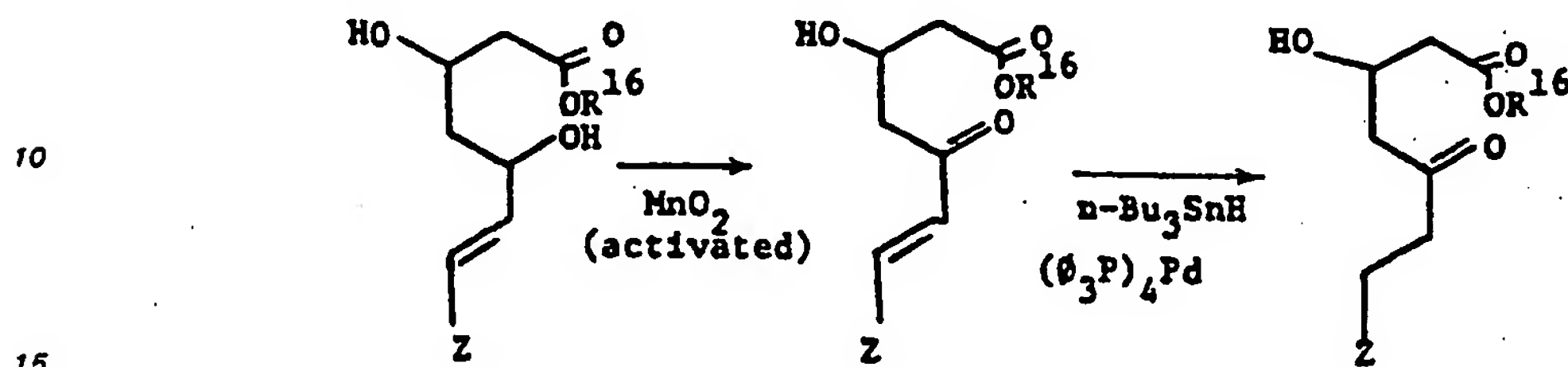
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wherein R^{16} is C_{1-4} alkyl, especially methyl. After protecting the 4-hydroxyl of the lactone with a dimethyl-*tert*-butylsilyl group and preparing an alkyl ester by known procedures, the resulting 5-hydroxy of the open-chain acid is oxidized to the ketone. Suitable oxidizing agents include: pyridinium chlorochromate in a chlorinated alkane such as methylene chloride or chloroform at about 0° to about 25°C for about 1 to 4 hour; oxalyl chloride in dimethylsulfoxide at about -70° to about -40°C for about 0.25 to 0.5 hours; trifluoroacetic anhydride in dimethylsulfoxide at about -70° to -40°C for about 0.25 to 0.5 hour; and pyridinium dichromate in dimethyl formamide at 0° to 25°C for 1 to 8 hours.

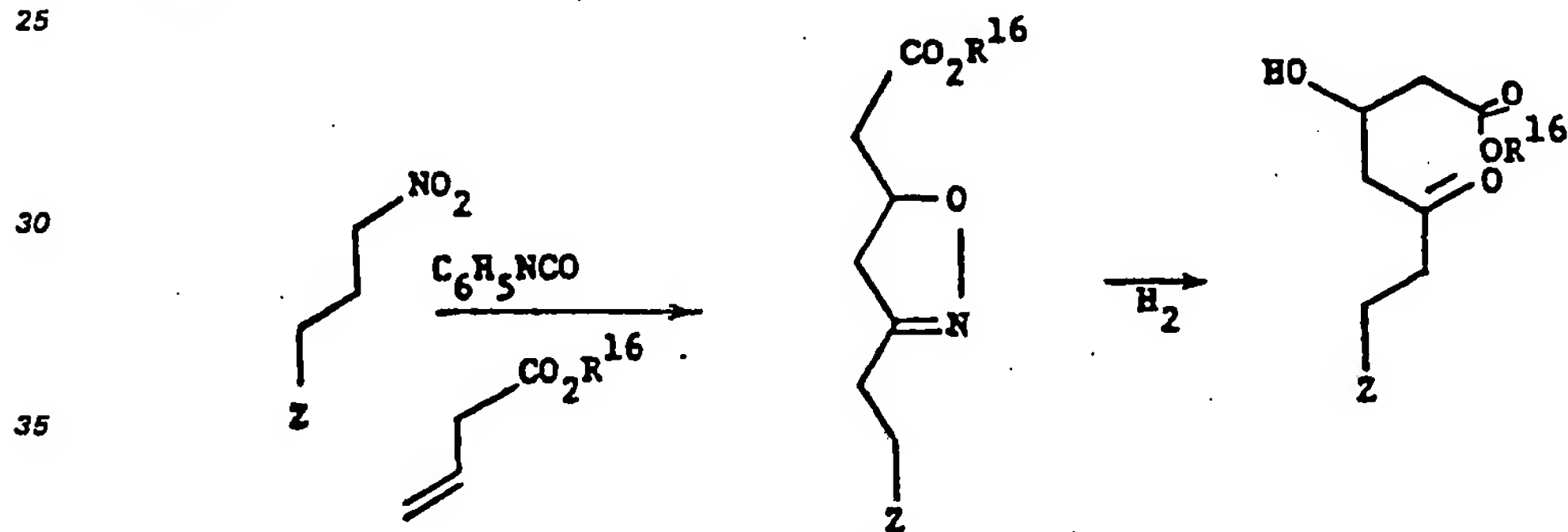
The silyl ether group is then hydrolyzed by treatment with acetic acid and tetrabutylammonium fluoride in tetrahydrofuran.

A related procedure is available for preparing compounds of this invention wherein E represents $-\text{CH}_2-\text{CH}_2-$. It obviates the need for protection of the 3-hydroxy group before oxidizing the 5-hydroxy and is represented as follows:



In the first step the dihydroxy compound is treated with activated manganese dioxide in a chlorinated hydrocarbon such as chloroform, methylene chloride, 1,2-dichloroethane or the like at about 0°C to 40°C preferably at ambient temperature for about 15 to 30 hours. The 5-oxo compound produced is then treated with tri-*n*-butyltin hydride and tetrakis(triphenylphosphine)palladium(0) in an ethereal solvent such as ether, THF, 1,2-dimethoxyethane or the like, at about ambient temperature for about 15 to 30 hours.

Alternatively, if the 3-hydroxy-5-oxo-carboxylic acid moiety is being synthesized, the 5-oxo group is realized directly by a process which is another embodiment of this invention and which is exemplified as follows:



The nitro compound is treated with a C₁₋₄alkyl 3-butenate, preferably methyl 3-butenate, and an aromatic isocyanate such as *p*-toluoyl isocyanate, *p*-chlorophenyl isocyanate, phenyl isocyanate or the like, preferably the latter, and a bit of triethylamine as a catalyst in an inert organic solvent such as toluene, benzene, xylene, or the like at about 15 to 30°C, preferably about room temperature for about 5 to about 24 hours.

The resulting isoxazoline is reduced catalytically with palladium on carbon, platinum oxide or the like in an inert organic solvent such as a C₁₋₃alkanol, acetic acid or the like containing a little water in the presence of boric acid at about 15 to 30°C and about 1-2 atmospheres of hydrogen pressure for about 1 to 6 hours.

The ester resulting from either of the foregoing synthetic schemes is readily saponified to the corresponding carboxylic acid salt by treatment with aqueous alkali such as potassium or sodium hydroxide to form the potassium or sodium salt respectively or with a quaternary ammonium hydroxide of formula HONR³R⁴R⁵R⁶ wherein none of the R groups is hydrogen to form the quaternary ammonium salt.

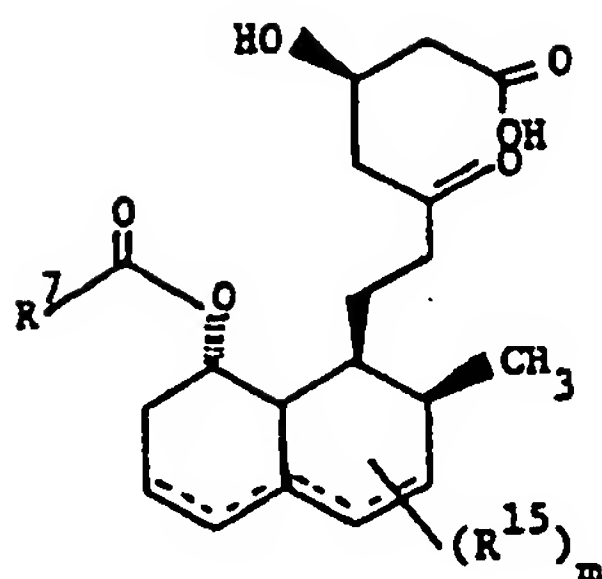
Acidifying any of these salts with a mineral acid results in the formation of the free carboxylic acid.

The acids are readily converted back to salts by treatment with the appropriate base or to esters by treatment with a C₁₋₃alkanol in the presence of a catalytic amount of an acid such as hydrogen chloride at about 50 to 100°C for about 3 to 6 hours.

The previously described salts are converted back to esters by treatment with an alkyl halide such as 2,3-dihydroxypropyl iodide in an aprotic solvent such as *N,N*-dimethylformamide, *N*-methylpyrrolidone or hexamethylphosphoramide at about 25 to 100°C for about 18 to 36 hours.

Those compounds, wherein Z is of the subtype (4), i.e., in which the polyhydronaphthalene moiety is substituted with hydroxy or oxo, halo or alkoxy are prepared from the corresponding substrate in which the 5-oxo group of the heptenoic acid is already in place. The processes, as applied to the 5-hydroxy analogs or the corresponding lactones, are disclosed in EP application 76601, British patents 2,111,052 and 2,075,013, EP application 74222, and Japanese published applications J58010572 and J57155995. Using those processes there are produced the following compounds:

0 142 146



Double Bonds	R^7	$(R^{15})_m$
3,4:4a,5	1-methylpropyl	6-OH
3,4:4a,5	1,1-dimethylpropyl	6-OH
4,4a	1-methylpropyl	3-OH, 5-OH
4,4a	1,1-dimethylpropyl	3-OH, 5-OH
4,4a:5,6	1-methylpropyl	3-OH
4,4a:5,6	1,1-dimethylpropyl	3-OH
-	1-methylpropyl	6-OH
-	1,1-dimethylpropyl	6-OH
-	1-methylpropyl	3-OH
-	1,1-dimethylpropyl	3-OH
4,4a	1-methylpropyl	6-OH
4,4a	1,1-dimethylpropyl	6-OH
4,4a	1-methylpropyl	3-OH
4,4a	1,1-dimethylpropyl	3-OH
4a,5	1-methylpropyl	6-OH
4a,5	1,1-dimethylpropyl	6-OH
4a,5	1-methylpropyl	3-OH
4a,5	1,1-dimethylpropyl	3-OH
4,4a	1-methylpropyl	3-OH, 5=O
4,4a	1,1-dimethylpropyl	3-OH, 5=O
4,4a	1-methylpropyl	3=O, 5=O
4,4a	1,1-dimethylpropyl	3=O, 5=O
-	1-methylpropyl	3-OH, 5-OH
-	1,1-dimethylpropyl	3-OH, 5-OH
4,4a	1-methylpropyl	3-Cl, 5-Cl
4,4a	1,1-dimethylpropyl	3-Cl, 5-Cl
4,4a	1-methylpropyl	3-OCH ₃ , 5-OH
4,4a	1,1-dimethylpropyl	3-OCH ₃ , 5-OH
4,4a	1-methylpropyl	3-OC ₂ H ₅ , 5-OH
4,4a	1,1-dimethylpropyl	3-OC ₂ H ₅ , 5-OH
4,4a	1-methylpropyl	3-OC ₄ H ₉ , 5-OH
4,4a	1,1-dimethylpropyl	3-OC ₄ H ₉ , 5-OH
4,4a	1-methylpropyl	6-CH ₃ , 3-OH, 5-OH
4,4a	1,1-dimethylpropyl	6-CH ₃ , 3-OH, 5-OH

The novel pharmaceutical composition of this invention comprises at least one of the compounds of formula I in association with a pharmaceutical vehicle or diluent. The pharmaceutical composition can be formulated in a classical manner utilizing solid or liquid vehicles or diluents and pharmaceutical additives of a type appropriate to the mode of desired administration. The compounds can be administered by an oral route, for example, in the form of tablets, capsules, granules or powders, or they can be administered by a parenteral route in the form of injectable preparations.

A typical capsule for oral administration contains active ingredients (25 mg), lactose (75 mg) and magnesium stearate (15 mg). The mixture is passed through a 60 mesh sieve and packed into a No. 1 gelatin capsule.

A typical injectable preparation is produced by aseptically placing 25 mg of a water soluble salt of sterile active ingredient into a vial, aseptically freeze-drying and sealing. For use, the contents of the vial are mixed with 2 ml of physiological saline, to produce an injectable preparation.

The novel method of treating atherosclerosis, familial hypercholesterolemia, or hyperlipemia of this invention comprises administration of an effective antihypercholesterolemic amount of a compound of Formula I to a patient in need of such treatment.

The dose to be administered depends on the unitary dose, the symptoms, and the age and the body weight of the patient. A dose for adults is preferably between 20 and 2,000 mg per day, which can be administered in a single dose or in the form of individual doses from 1—4 times per day.

The compounds of this invention also have useful antifungal activities. For example, they may be used to control strains of *Penicillium sp.*, *Aspergillus niger*, *Cladosporium sp.*, *Cochliobolus miyabeorus* and *Helminthosporium cynodnotis*. For those utilities they are admixed with suitable formulating agents, powders, emulsifying agents or solvents such as aqueous ethanol and sprayed or dusted on the plants to be protected.

This invention can be illustrated by the following examples.

Example 1

7-[2(S),6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-hydroxy-5-oxoheptanoic acid

Step A: Preparation of 6(R)-[2-(8(S)-(2(S)-methylbutyryloxy)-2(S),6(R)-dimethyl-1,2,6,7,8,8a(R)-hexahydronaphthyl-1(S))-ethyl]-4(R)-(dimethyl-*tert*-butylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one

Mevinolin (4.04 g, 0.01 mol) was dissolved in 25 ml of dry dimethylformamide (DMF) and treated with 2.7 g (0.04 mol) of imidazole and 3 g (0.02 mol) of dimethyl-*tert*-butylsilyl chloride, and the solution was stirred under nitrogen overnight. The mixture was poured into 200 ml of ether, washed with 2 × 50 ml of water, 1 × 25 ml of 1N hydrochloric acid, 1 × 25 ml of saturated aqueous sodium carbonate and 2 × 50 ml of brine, dried over $MgSO_4$ and concentrated to dryness. The residue was chromatographed on a "Still" column of silica gel (6.0 × 17.7 cm, 230—400 mesh) by elution with 45% ether in hexane (V/V) collecting 20 ml fractions. The fractions containing the product (21—52) were combined and concentrated to dryness to give 5.2 of oil.

Step B: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-(tert-butylidimethylsilyloxy)-5(R)-hydroxyheptanoate

The silyl ether from Step A (1.03 g, 0.002 mol) was dissolved in 10 ml of methanol, treated with 2 ml of 1N aqueous sodium hydroxide and the mixture was stirred for 2 hours at room temperature. The methanol was evaporated under reduced pressure and the residue was freed of water by azeotropic distillation of 4 × 10 ml of toluene. The solid residue was dissolved in 5 ml of dry DMF, treated with 300 μ l, (0.68 g, 0.0048 mol) of methyl iodide and the mixture was stirred overnight at room temperature. The mixture was poured into 100 ml of ether and washed with 20 ml of water and 20 ml of brine, dried ($MgSO_4$) and concentrated to dryness to give 1.0 g of residue (contained DMF). This material was chromatographed on a "Still" column of silica gel (6.0 × 17.7 cm, 230—400 mesh) by elution with 45% ether in hexane (V/V) collecting 20 ml fractions. Fractions 32—50 containing the major component were combined and concentrated to dryness to give 576 mg of oily product.

Step C: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-(tert-butylidimethylsilyloxy)-5-oxoheptanoate

The ester from Step B (586 mg, 0.001 mol) was dissolved in 10 ml of methylene chloride and cooled to 0°C. Pyridine chlorochromate (0.56 g, 0.0026 mol) was added and the stirred mixture was allowed to warm spontaneously over 2 hours. Additional pyridine chlorochromate (224 mg, 0.001 mol) was added and stirring was continued another hour. The methylene chloride was evaporated *in vacuo*. The residue was suspended in 5 ml. ether, placed on top of a 4 × 40 cm column of silica gel (70—230 mesh) and eluted with 40% ether in hexane (V/V) collecting 15 ml fractions. Fractions 10—23 were combined and concentrated to 130 mg. of oily product.

Step D: Preparation of Methyl 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-hydroxy-5-oxoheptanoate

The silyl ether from Step C (230 mg, 0.00024 mol) was dissolved in 5 ml of tetrahydrofuran (THF) and

treated with 54 μ l, (0.057 g, 0.00095 mol) of acetic acid and 710 μ l (1M in THF, 0.00071 mol) of tetrabutylammonium fluoride ($\text{Bu}_4\text{N}^+\text{F}^-$) and the mixture was stirred overnight at room temperature.

Another 57 μ l of acetic acid and 710 μ l of $\text{Bu}_4\text{N}^+\text{F}^-$ were added and stirring was continued an additional 24 hours. The mixture was poured into 100 ml of ether and washed with 1 \times 5 ml of 1N hydrochloric acid, 1 \times 10 ml of saturated aqueous sodium bicarbonate and 2 \times 10 ml of brine and dried (MgSO_4). Concentration to dryness gave 120 mg of an oil. The oil was chromatographed on a "Still" column of silica gel (1.5 \times 17.7 cm, 230—400 mesh) by elution with 5% acetone in methylene chloride (v/v) collecting 5 ml fractions. Fractions 12—20 containing the product were combined and concentrated to dryness to give 53 mg of solid (m.p. 64—66°C). Recrystallization of a sample from hexane gave material with m.p. 67—68°C.

Analysis for $\text{C}_{25}\text{H}_{38}\text{O}_6$ (434.55):

Calc: C, 69.09; H, 8.81.

Found: C, 69.30; H, 9.38.

Step E: Preparation of 7-[2(S), 6(R)-Dimethyl-8(S)-(2(S)-methylbutyryloxy)-1,2,6,7,8,8a(R)-hexahydro-1(S)-naphthyl]-3(R)-hydroxy-5-oxoheptanoic acid

The ester from Step D (43 mg, 0.0001 mol) was dissolved in 5 ml of methanol and treated with 2 ml of 0.1N sodium hydroxide (0.0002 mol) and stirred overnight at room temperature. The methanol was evaporated *in vacuo* and the residue was acidified with 1N hydrochloric acid and extracted with ether. The ether extract was washed with 3 \times 10 ml of brine and dried over MgSO_4 . Concentration to dryness provided 36 mg of solid which after recrystallization from ether/hexane had m.p. 102—103°C.

Analysis for $\text{C}_{24}\text{H}_{36}\text{O}_6$ (420.53):

Calc: C, 68.54; H, 8.63.

Found: C, 68.57; H, 8.88.

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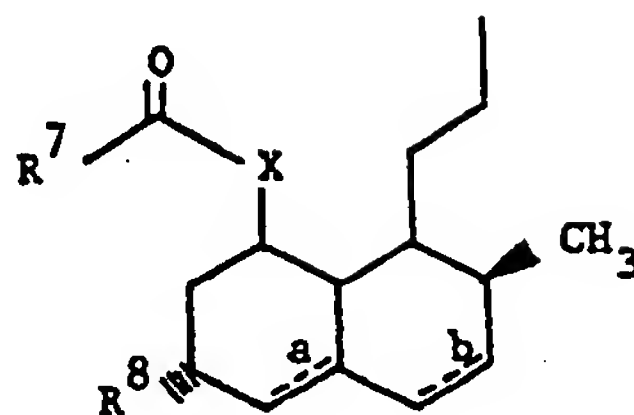


TABLE I

1)

$$\begin{array}{c} | \\ E \\ | \\ Z \end{array}$$

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 R^8

X

a

b

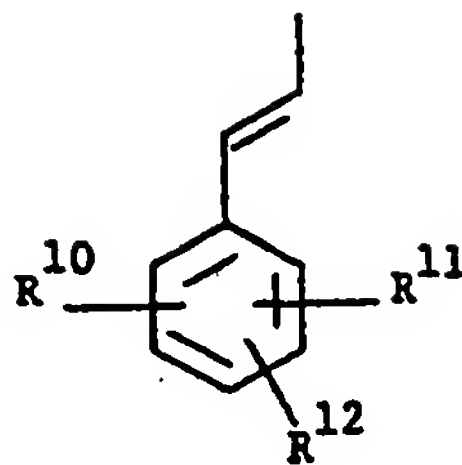
	R^8	X	a	b
2(S)-methylbutyryl	$-CH_3$	O	single	double
2(S)-methylbutyryl	$-CH_3$	O	single	single
2(R)-methylbutyryl	$-CH_3$	O	double	double
2,2-dimethylbutyryl	$-CH_3$	O	double	double
2,2-dimethylbutyryl	$-CH_3$	O	single	double
2,2-dimethylbutyryl	$-CH_3$	O	single	single
acetyl	$-CH_3$	O	double	double
2(S)-methylbutyryl	H	O	single	single
2,2-dimethylbutyryl	H	O	double	double
2,2-dimethylbutyryl	H	O	single	single
2,2-dimethylbutyryl	$-CH_3$	NH	single	single
2-methyl-2-ethylbutyryl	$-CH_3$	NH	single	single
2-methylbutyryl	$-CH_3$	NH	single	single
4-fluorobenzoyl	$-CH_3$	NH	single	single
4-fluorophenylacetyl	$-CH_3$	NH	single	single
4-tert-butylbenzoyl	$-CH_3$	NH	single	single
acetyl	$-CH_3$	NH	double	double
acetyl	$-CH_3$	NCH ₃	single	single
2,2-dimethylbutyryl	$-CH_3$	NCH ₃	single	single
2,2-dimethylbutyryl	$-CH_3$	NH	double	double

(2)

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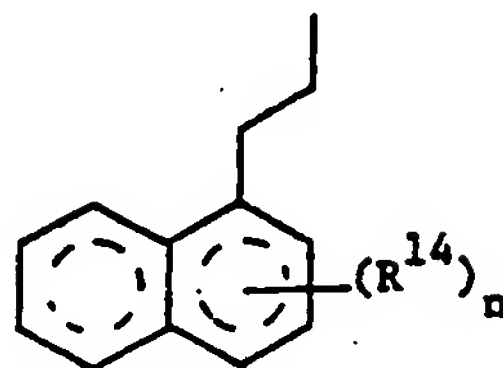
	R^{10}	R^{11}	R^{12}
15	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
	6-(4-fluorophenyl)-	2-chloro	4-chloro
	6-(4-chlorophenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-chloro	4-chloro
20	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	4-methyl
	6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
25	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
	6-(4-fluorophenyl)-	2-methyl	4-methyl
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
30	6-(4-fluorobenzoyloxy)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)	2-chloro	4-methyl

35

3)



=



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	n	R^{14}	
45	1	2-methyl	naphthyl
	0	-	naphthyl
	2	2,6-dimethyl	naphthyl
50	1	2-methyl	5,6,7,8-tetra- hydronaphthyl

55

Example 2

7-(4'-Fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoic acid

Step A: Preparation of Methyl 3-(4'-Fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)propionate

A solution of 1.716 g (13 mmol) of dimethyl malonate in 5 ml of DMF was added dropwise to a stirred suspension of sodium hydride (50% oil dispersion, 0.624 g, 13 mmol) in 15 ml of DMF and stirring was continued under nitrogen for 0.5 hour. The mixture was treated with ice bath cooling, with a solution of 3.1 g (11.8 mmol) of 2-chloromethyl-4'-fluoro-3,3',5-trimethyl-1,1'-biphenyl in 10 ml of DMF. The resulting mixture was stirred at 0°C for 10 minutes, at room temperature for 0.5 hour, and heated on a steam bath for 1 hour. Sodium chloride (0.759 g, 13 mmol) and 0.234 ml (13 mmol) of water were added to the reaction mixture and it was heated at reflux for 16 hours. The reaction mixture was cooled, poured into cold water and extracted with ether twice. The combined extracts were washed with dilute hydrochloric acid, dried

over MgSO_4 , filtered and concentrated to dryness *in vacuo* to give 3.42 (11.38 mmol, 96%) of the desired product as a brown oil which was used directly in the next step without purification.

nmr (CDCl_3) δ : 2.27 (6H, a methyl singlet and a methyl doublet), 2.3 (2H, m), 2.34 (3H, s), 2.9 (2H, m), 3.60 (3H, s), 6.84 (H, bs), 7.1—7.2 (4H, m).

Step B: Preparation of 3-(4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)propanol

A solution of 3.42 g (11.4 mmol) of the ester from Step A in 25 ml of ether was added dropwise to a stirred suspension of 0.38 g (10 mmol) of lithium aluminum hydride in 75 ml of ether at 0°C under nitrogen. After completion of the addition, the mixture was stirred at room temperature for 15 minutes, refluxed for 1 hour, cooled in ice and treated with successive additions of 0.4 ml of water, 0.35 ml of 20% (w/v) aqueous sodium hydroxide and 1.1 ml of water. The resulting mixture was stirred at 0°C for 0.5 hour, treated with anhydrous MgSO_4 , stirred for 15 minutes and filtered. The filtrate was concentrated *in vacuo* to give 3.08 g (11.3 mmol) (99%) of pale yellow oily product which was used directly in the next step without purification.

nmr (CDCl_3) δ : 1.45—1.7 (2H, m), 2.25 (6H, s), 2.33 (3H, s), 2.45—2.7 (2H, m), 3.45 (2H, t, $J=6\text{Hz}$), 6.85 (H, bs), 6.95—7.2 (4H, m).

Step C: Preparation of 2-(3-Bromopropyl)-4'-fluoro-3,3',5-trimethyl-1,1'-biphenyl

A solution of 1.08 g (4 mmol) of PBr_3 in 10 ml of ether was added dropwise to a stirred solution of 3.08 g (11.3 mmol) of the alcohol from Step B in 40 ml of ether at 0°C . The mixture was stirred at room temperature for 1 hour, refluxed for 0.5 hour, cooled to room temperature, poured into ice water and extracted with ether. The extract was washed with water and saturated aqueous sodium bicarbonate, dried over MgSO_4 , filtered and evaporated to dryness *in vacuo*. The residue was purified by flash chromatography on silica gel (230—400 mesh) by elution with methylene chloride/hexane (1:3, v/v). Combination and evaporation of the appropriate fractions gave the desired bromide as a pale yellow oil, 1.9 g, 5.67 mmol, 48% overall Steps A, B and C).

nmr (CDCl_3) δ : 1.7—2.0 (2H, m), 2.27 (6H, a methyl singlet and a methyl doublet), 2.35 (3H, s), 2.55—2.8 (2H, m), 3.23 (2H, t, $J=6\text{Hz}$), 6.85 (H, bs), 6.95—7.2 (4H, m).

Step D: Preparation of 4'-Fluoro-3,3',5-trimethyl-2-(3-nitropropyl)-1,1'-biphenyl

A solution of 1.90 g (5.66 mmol) of the bromopropyl compound from Step C in 5 ml of ether was added to a stirred suspension of 1.31 g (8.5 mmol) of silver nitrite in 5 ml of ether at 0°C . The resulting mixture was stirred under nitrogen at 0°C for 7 hours, warmed to room temperature and stirred for an additional 16 hours. Another 1.0 g of silver nitrite was added and stirring was continued for another 20 hours.

The reaction mixture was filtered and the filtrate was concentrated to leave a residue which was purified by flash chromatography on silica gel (230—400 mesh) by elution with methylene chloride/hexane (1:4, v/v) to give, first, the recovered starting bromide, then the desired product, (0.64 g, 2.12 mmol, 78%).

nmr (CDCl_3) δ : 1.8—2.2 (2H, m), 2.30 (6H, a methyl singlet and a methyl doublet), 2.33 (3H, s), 2.5—2.7 (2H, m), 4.18 (2H, t, $J=6\text{Hz}$), 6.88 (H, bs), 7.0—7.2 (4H, m). IR (neat) 1550, 1500 cm^{-1} .

Step E: Preparation of Methyl 3-[2-(4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)ethyl]-4,5-dihydro-5-isoxazoleacetate

A solution of 0.1 g (1.0 mmol) of methyl 3-butenate and 0.174 ml (1.6 mmol) of phenyl isocyanate in 1 ml of toluene was added with stirring to a solution of 0.240 g (0.8 mmol) of the nitropropyl compound from Step D and 2 drops of triethylamine in 1 ml of toluene. The resulting mixture was stirred at room temperature for 3 hours. Additional quantities of methyl 3-butenate (0.1 ml), triethylamine (0.1 ml) and phenyl isocyanate (0.15 ml) were added successively and stirring was continued overnight (18 hours). The mixture was filtered and the filtrate was concentrated *in vacuo* to a residue which was purified by flash chromatography on silica gel (230—400 mesh), first being eluted with methylene chloride to remove the impurities. Continued elution with acetone/methylene chloride (1:50, v/v) gave the desired product (0.218 g, 0.57 mmol, 71%) as a pale viscous oil.

nmr (CDCl_3) δ : 2.28 (6H, s), 2.32 (3H, s), 2.2—3.0 (6H, m), 3.70 (3H, s), 4.6—5.0 (H, m), 6.85 (H, bs), 7.0—7.2 (4H, m). IR (neat) 1735 cm^{-1} .

Analysis calculated for $\text{C}_{23}\text{H}_{26}\text{FNO}_3$: C, 72.04; H, 6.83; N, 3.65.

Found: C, 72.35; H, 6.99; N, 3.88.

Step F: Preparation of Methyl 7-(4'-fluoro-3,3',5-trimethyl[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoate

A mixture of 0.1 g (0.26 mmol) of the isoxazoline from Step E, 50 mg of 10% palladium on carbon catalyst and 48 mg (0.78 mmol) of boric acid in 3 ml of methanol and 0.3 ml of water was stirred under hydrogen (1 atmosphere) at room temperature for 2.5 hours. The mixture was filtered and the filtrate was poured into brine and extracted with ether. The ethereal extract was washed with 5% (w/v) aqueous sodium bicarbonate solution, dried (MgSO_4), filtered and evaporated to dryness to give 92 mg (0.23 mmol, 89%) as a pale yellow oil.

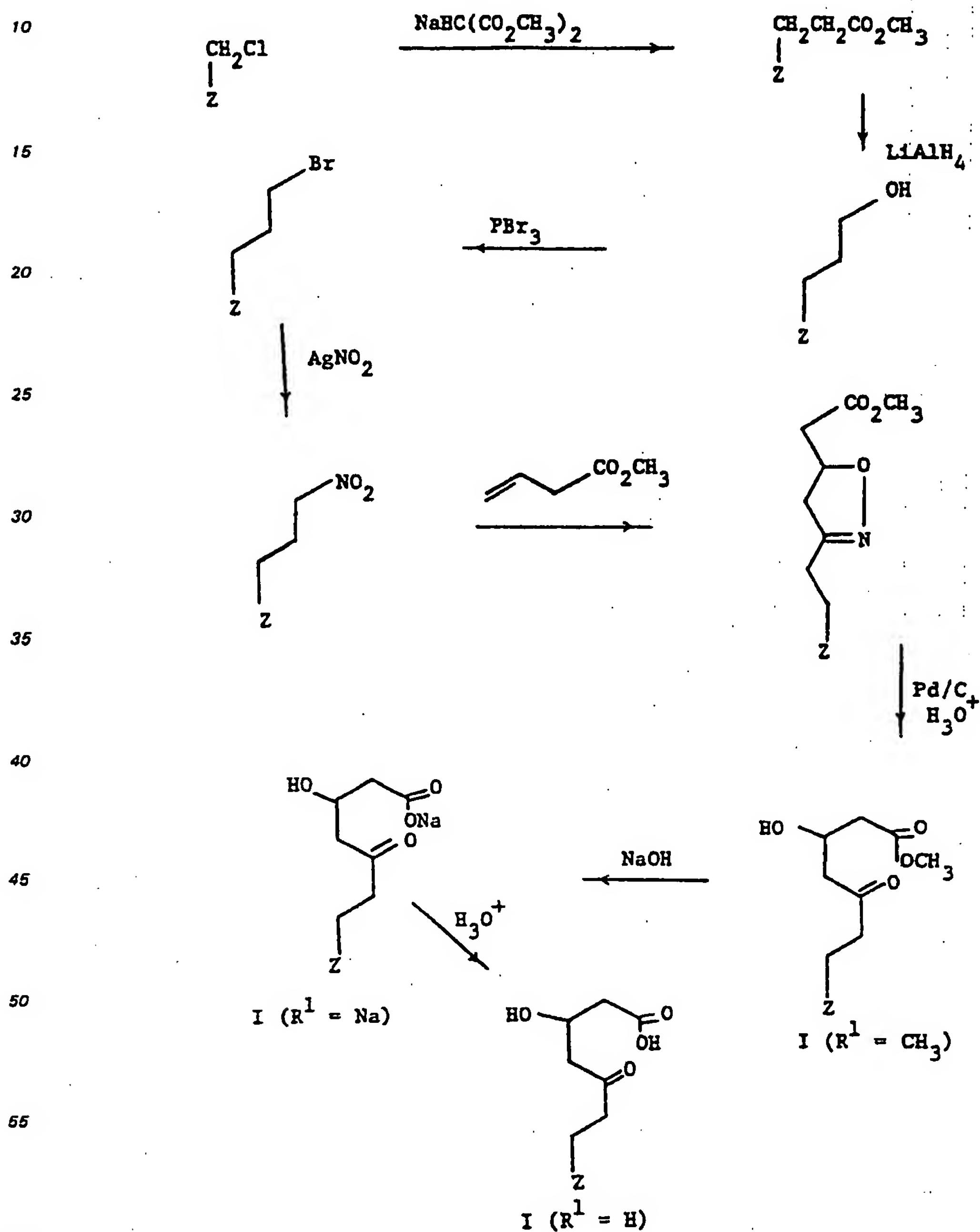
nmr (CDCl_3) δ : 2.30 (6H, a methyl singlet and a methyl doublet), 2.33 (3H, s), 2.35—2.5 (6H, m), 2.75—2.85 (2H, m), 3.30 (H, d), 3.70 (3H, s), 4.37 (H, m), 6.83 (H, bs), 6.95—7.1 (4H, m). IR (neat) 3450, 1710 cm^{-1} .

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Step G: Preparation of 7-(4'-fluoro-3,3',5-trimethyl-[1,1'-biphenyl]-2-yl)-3-hydroxy-5-oxoheptanoic acid

Employing the procedure substantially as described in Example 1, Step E, the ester from Step G of this Example 2 is saponified to the subject 5-keto acid.

Employing the procedure substantially as described in Example 2, Steps A through G, but substituting
 5 for the chloromethylbiphenyl employed in Step A thereof, equimolar amounts of the chloromethyl compounds described in Table II, there are produced the 5-keto esters, salts and acids also described in Table II in accordance with the following reaction sequence:



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TABLE II

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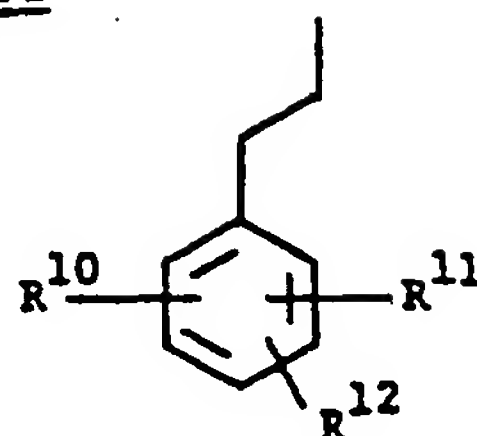
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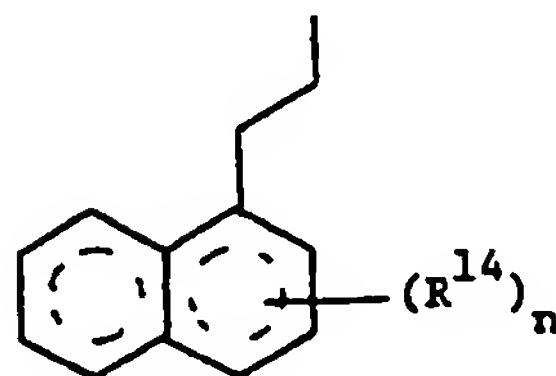
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	R ¹⁰	R ¹¹	R ¹²
	6-(4-fluorophenyl)-	2-chloro	4-chloro
	6-(4-chlorophenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	4-methyl
	6-(3,4-dimethylphenyl)-	2-chloro	4-chloro
	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
	6-(4-fluorophenyl)-	2-methyl	4-methyl
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
	6-(4-fluorobenzyloxy)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-methyl



=



n	R ¹⁴	
1	2-methyl	naphthyl
0	-	naphthyl
2	2,6-dimethyl	naphthyl
1	2-methyl	5,6,7,8-tetra-
		hydronaphthyl

Example 3

7-(2,4-Dichlorophenyl)-3-hydroxy-5-oxoheptanoic acid

Step A: Preparation of Methyl 7-(2,4-Dichlorophenyl)-3-hydroxy-5-oxo-6-heptenoate

Activated manganese dioxide (40 g) was added to a solution of methyl 7-(2,4-dichlorophenyl)-3,5-dihydroxy-6-heptenoate (6.8 g, 21.3 mmol) in chloroform (600 mL) and the black suspension was vigorously stirred at ambient temperature for 20 hours. After filtration and evaporation of the solvent the residual amber oil (4.5 g, 1 major spot on TLC with F₁ 0.61 on Whatman MK6F silica using CHCl₃—MeOH,

19:1 as eluent) was chromatographed on a Still column to obtain the product (3.9 g, 58%) as a pale yellow oil which solidified on standing, m.p. 77–79°C;

nmr (CDCl₃) δ: 2.57 (2H, d, J=6Hz, —CH₂CO₂—), 2.93 (2H, d, J=6Hz, —CH₂—CO—), 3.70 (3H, s, —CO₂CH₃), 4.4–4.8 (H, m, —CH(OH)—), 6.67 (H, d, J=16 Hz, =CH—CO), 7.1–7.7 (3H, m, ArH), 7.93 (H, d, J=16 Hz, =CH).

Analysis for C₁₄H₁₄Cl₂O₄.

Calc: C, 53.02; H, 4.45.

Found: C, 53.25; H, 4.50.

10 **Step B: Preparation of Methyl 7-(2,4-Dichlorophenyl)-3-hydroxy-5-oxoheptanoate**

Tributyltin hydride (450 μL, 1.7 mmol) was added dropwise over 1½ hours to a stirred solution of the ene-one ester from Step A (320 mg, 1 mmol) and tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.03 mmol) in dry THF (5 mL) at ambient temperature under N₂. After standing at 20°C overnight the light-brown solution was distributed between water (100 mL) and ether (150 mL). The organic layer was separated and washed with water (2 × 100 mL), dried and evaporated. The residual oil (1 major spot on TLC with R_f 0.39 vis-a-vis 0.35 for the starting ene-one ester on Whatman MK6F silica using CHCl₃—NeOH; 99:1 as eluent) was chromatographed on a Still column to obtain the product (260 mg, 81%) as a pale amber gum;

nmr (CDCl₃) δ: 2.5–2.525 (2H, m, —CH₂CO₂—), 2.57–2.73 (2H, m, —COCH₂C(OH)—), 2.77 (2H, t, J=7.5 Hz, AR—CH₂CH₂CO—), 2.98 (2H, t, J=7.5 Hz, AR—CH₂CH₂CO—), 3.71 (3H, s, —CO₂CH₃), 4.45–4.51 (H, m, —CH(OH)—).

Analysis for C₁₄H₁₆Cl₂O₄

Calc: C, 52.68; H, 5.05.

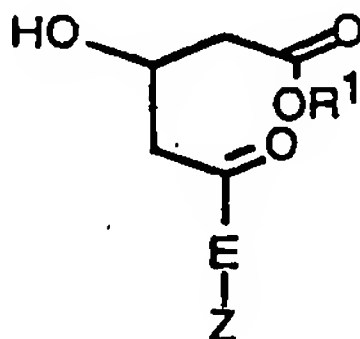
Found: C, 52.47; H, 5.20.

25 **Step C: Preparation of 7-(2,4-dichlorophenyl)-3-hydroxy-5-oxoheptanoic acid**

Employing the procedure substantially as described in Example 1, Step E, the ester from Step B of this Example 3 is saponified to the subject 5-oxo acid.

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. A compound of structural formula:



wherein:

R¹ is

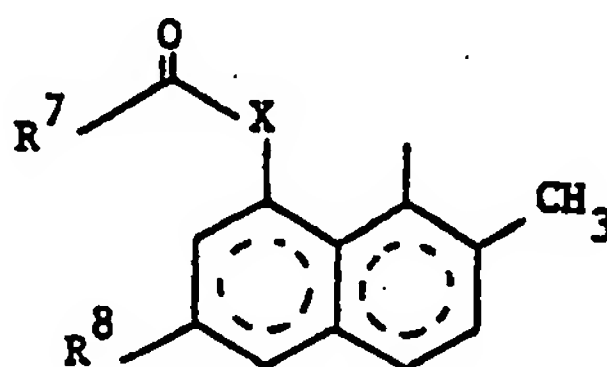
- 1) hydrogen,
- 2) C₁₋₄alkyl,
- 3) 2,3-dihydroxypropyl,
- 4) alkali metal cation, or
- 5) ammonium of formula



wherein R³, R⁴, R⁵ and R⁶ are independently hydrogen or C₁₋₄alkyl or two of R³, R⁴, R⁵ and R⁶ are joined together to form a 5- or 6-membered heterocycle with the nitrogen to which they are attached;

E is —CH₂CH₂—, —CH=CH—, or —(CH₂)₃—; and

Z is

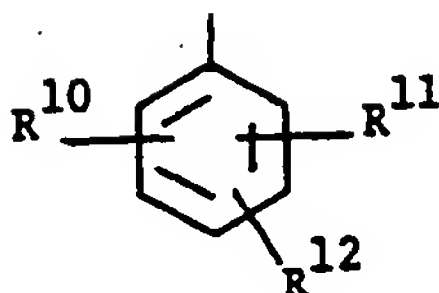


wherein the dotted lines represent all of the possible oxidation states of the bicyclic system, X is —O— or —NR⁹ wherein R⁹ is hydrogen or C₁₋₃alkyl;

R⁷ is C₂₋₈alkyl; and

R^8 is hydrogen or $-\text{CH}_3$;

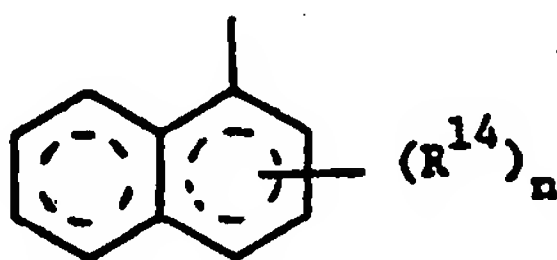
2)



wherein R^{10} , R^{11} and R^{12} are independently

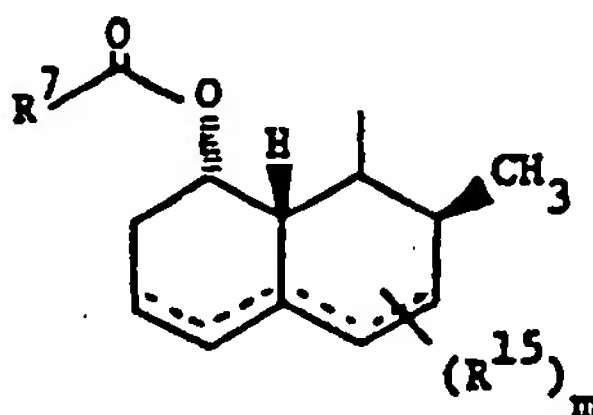
- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C_{1-4} alkyl,
- d) halo- C_{1-4} alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C_{1-4} alkoxy,
 - ii) C_{1-4} alkyl,
 - iii) C_{2-8} alkanoyloxy,
 - iv) halo- C_{1-4} alkyl, or
 - v) halo,
- f) OR^{13} wherein R^{13} is
 - i) hydrogen,
 - ii) C_{2-8} alkanoyl,
 - iii) benzoyl,
 - iv) phenyl,
 - v) halophenyl,
 - vi) phenyl- C_{1-3} alkyl, either unsubstituted or substituted with one or more of halogen, C_{1-4} alkoxy, C_{1-4} alkyl or halo- C_{1-4} alkyl,
 - vii) C_{1-9} alkyl,
 - viii) cinnamyl,
 - ix) halo- C_{1-4} alkyl,
 - x) allyl,
 - xi) C_{3-8} cycloalkyl- C_{1-3} alkyl, or
 - xii) adamantyl- C_{1-3} alkyl;

3)



wherein n is 0—2 and R^{14} is halo or C_{1-4} alkyl; and

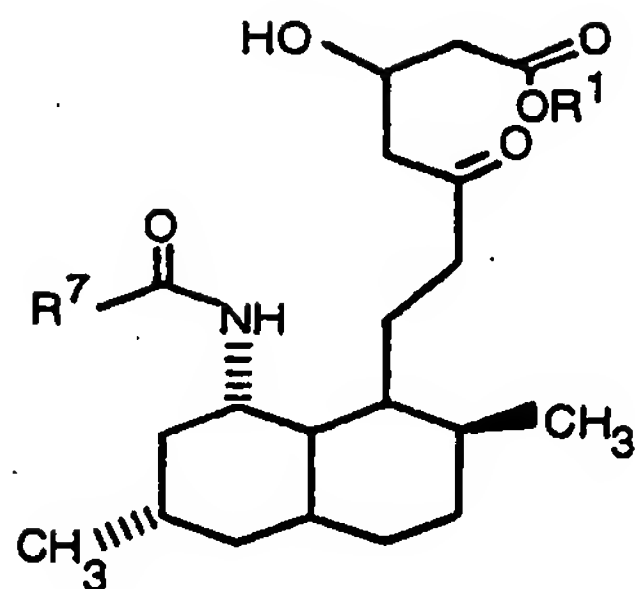
4)



wherein the dotted lines represent possible double bonds there being 0, 1 or 2 double bonds;
 m represents 1, 2 or 3; and
 R^{15} is

- 1) methyl,
- 2) hydroxy,
- 3) C_{1-4} alkoxy,
- 4) oxo, or
- 5) halo.

2. A compound of structural formula



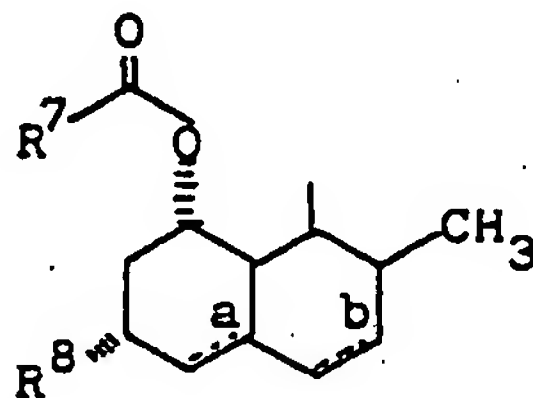
wherein R¹ is hydrogen, an alkali metal cation or an ammonium cation and wherein R⁷ is 4-fluorobenzoyl, 4-tert-butylbenzoyl or 4-fluorophenylacetyl.

3. The compound of Claim 1 wherein:

R¹ is hydrogen, an alkali metal cation or an ammonium cation;

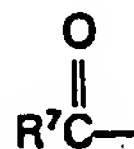
E is —CH=CH— or —CH₂CH₂—; and

Z is



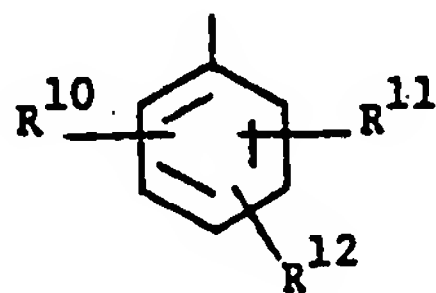
1)

wherein



is 2(S)-methylbutyryl or 2,2-dimethylbutyryl;

2)



wherein R¹⁰, R¹¹ and R¹² are independently

a) halogen,

b) C₁₋₄alkyl,

c) halo-C₁₋₄alkyl,

d) phenyl with 1 to 3 substituents selected from halo, C₁₋₄alkyl or C₁₋₄alkoxy,

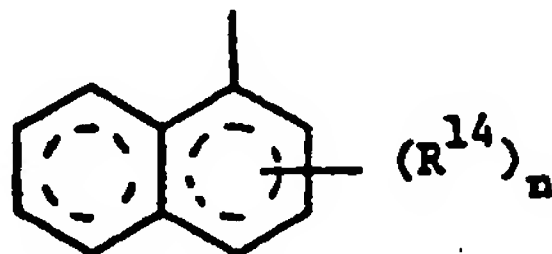
e) OR¹³, wherein R¹³ is

i) phenyl,

ii) halophenyl, or

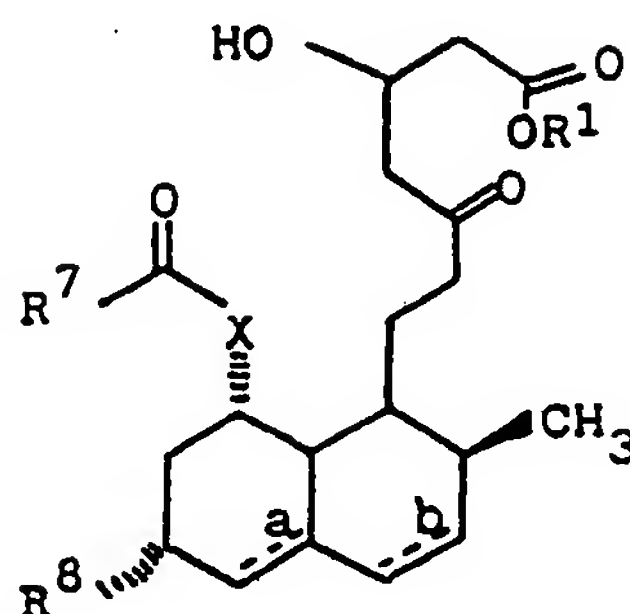
iii) phenyl-C₁₋₃ alkyl, either unsubstituted or substituted with one or more of halogen, C₁₋₄ alkoxy, C₁₋₄ alkyl or halo-C₁₋₄ alkyl; or

3)



wherein n is 0, 1 or 2, and R¹⁴ is methyl, and the ring system is naphthyl, or 5,6,7,8-tetrahydronaphthyl.

4. The compound of Claim 1 selected from:



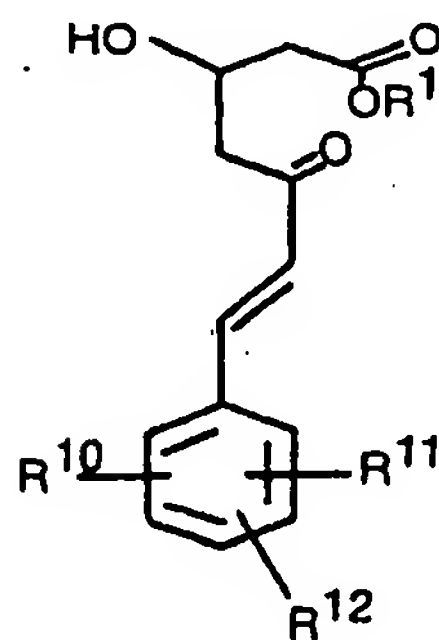
wherein R¹ is hydrogen, an alkali metal cation or an ammonium cation and wherein R⁷CO—, R⁸, X a and b have the following meanings:

	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^7\text{C}- \end{array}$	R ⁸	X	a*	b
	2(S)-methylbutyryl	—CH ₃	O	single	double
	2(S)-methylbutyryl	—CH ₃	O	single	single
	2(R)-methylbutyryl	—CH ₃	O	double	double
	2,2-dimethylbutyryl	—CH ₃	O	double	double
	2,2-dimethylbutyryl	—CH ₃	O	single	double
	2,2-dimethylbutyryl	—CH ₃	O	single	single
	acetyl	—CH ₃	O	double	double
	2(S)-methylbutyryl	H	O	double	double
	2(S)-methylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	H	O	double	double
	2,2-dimethylbutyryl	H	O	single	single
	2,2-dimethylbutyryl	—CH ₃	NH	single	single
	2-methyl-2-ethylbutyryl	—CH ₃	NH	single	single
	2-methylbutyryl	—CH ₃	NH	single	single
	acetyl	—CH ₃	NH	double	double
	acetyl	—CH ₃	NCH ₃	single	single
	2,2-dimethylbutyryl	—CH ₃	NCH ₃	single	single
	2,2-dimethylbutyryl	—CH ₃	NH	double	double

* When a = single bond, the rings are *trans*-fused.

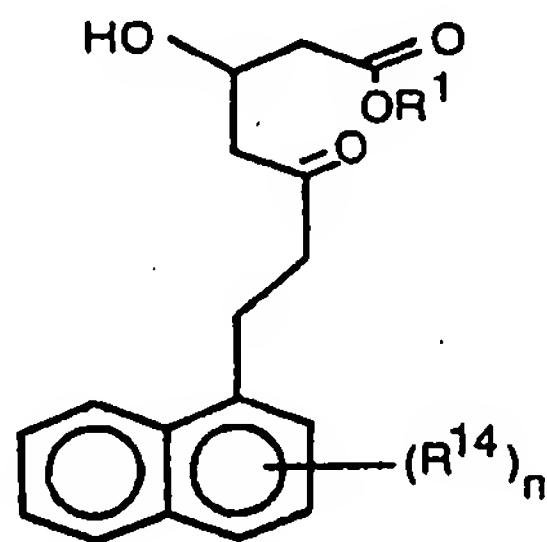
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5. The compound of claim 3 selected from:



R ¹⁰	R ¹¹	R ¹²
6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
6-(4-fluorophenyl)-	2-chloro	4-chloro
6-(4-chlorophenyl)-	2-chloro	4-chloro
6-(3,4-dichlorophenyl)	2-chloro	4-chloro
6-(4-fluoro-3-methylphenyl)	2-chloro	4-chloro
6-(3,4-dichlorophenyl)	2-methyl	4-methyl
6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
6-(4-fluorophenyl)	2-methyl	4-methyl
6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
6-(4-fluorobenzyloxy)	2-chloro	4-chloro
6-(4-fluoro-3-methylphenyl)-	2-chloro	4-methyl

6. The compound of claim 3 selected from:



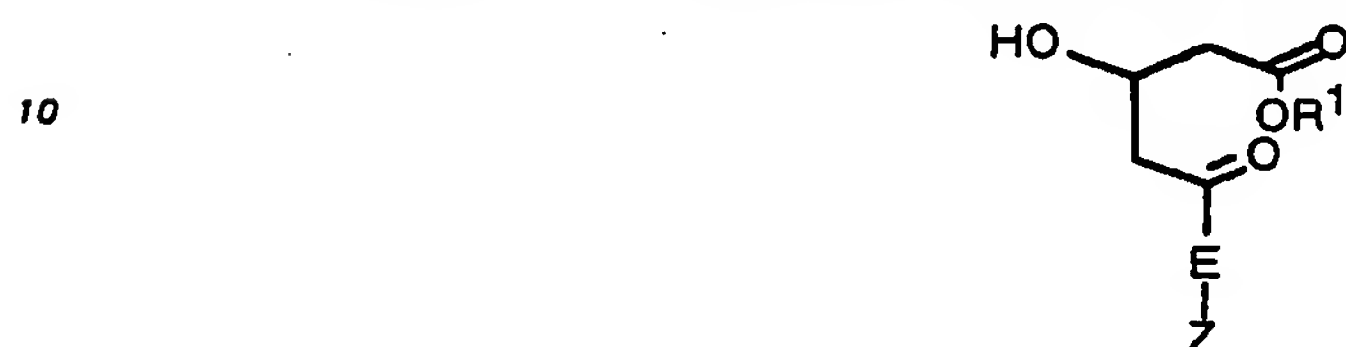
n	R ¹⁴	
1	2-methyl	naphthyl
0	—	naphthyl
2	2,6-dimethyl	naphthyl
1	2-methyl	5,6,7,8-tetrahydronaphthyl

7. An antihypercholesterolemic pharmaceutical composition comprising a pharmaceutical carrier and an effective antihypercholesterolemic amount of a compound as claimed in Claim 1 or 2.

8. The formulation of Claim 7 wherein the antihypercholesterolemic compound is as claimed in Claim 3.

9. The formulation of Claim 8 wherein the antihypercholesterolemic compound is as claimed in Claims 4, 5 or 6.

10. A process for the preparation of a compound of structural formula:



15 wherein R¹, E and Z have the meanings of R¹, E and Z 1), 2) and 3) in claim 1, which comprises treating a compound of structural formula:



wherein R¹⁶ is C₁-₄alkyl, with an oxidizing agent to produce the compound of structural formula:



40 followed by desilylation to produce the compound of structural formula:



50 followed by treatment with alkali to produce the product wherein R¹⁶ is an alkali metal cation, followed by acidification to produce the compound wherein R¹⁶ is a hydrogen ion.

Claims for the Contracting State: AT

55 1. A process for the preparation of a compound of structural formula:



wherein:

65 R¹ is
1) hydrogen,

- 2) C₁₋₄alkyl,
- 3) 2,3-dihydroxypropyl,
- 4) alkali metal cation, or
- 5) ammonium of formula

5



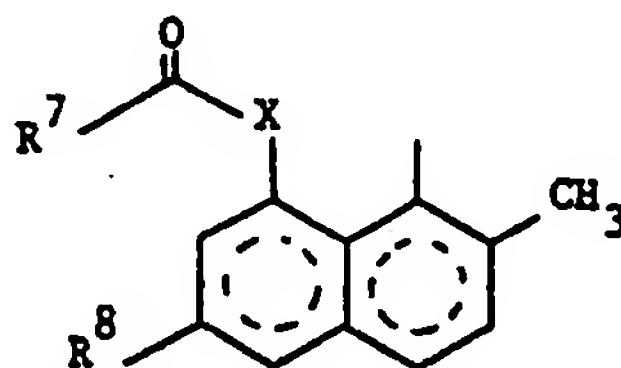
wherein R³, R⁴, R⁵ and R⁶ are independently hydrogen or C₁₋₄alkyl or two of R³, R⁴, R⁵ and R⁶ are joined together to form a 5- or 6-membered heterocycle with the nitrogen to which they are attached;

10 E is —CH₂CH₂—, —CH=CH—, or —(CH₂)₃—; and
Z is

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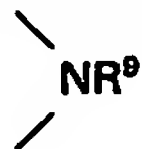
1)

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wherein the dotted lines represent all of the possible oxidation states of the bicyclic system, X is —O— or

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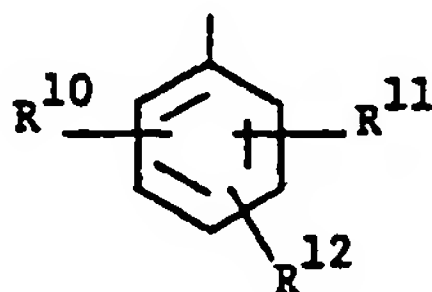
wherein R⁹ is hydrogen or C₁₋₃alkyl;

R⁷ is C₂₋₈alkyl; and

R⁸ is hydrogen or —CH₃;

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2)



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wherein R¹⁰, R¹¹ and R¹² are independently

a) hydrogen,

b) halogen, such as bromo, chloro or fluoro,

c) C₁₋₄alkyl,

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d) halo-C₁₋₄alkyl,

e) phenyl either unsubstituted or substituted with one or more of

i) C₁₋₄alkoxy,

ii) C₁₋₄alkyl,

iii) C₂₋₈alkanoyloxy, or

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iv) halo-C₁₋₄alkyl,

v) halo,

f) OR¹³ wherein R¹³ is

i) hydrogen,

ii) C₂₋₈alkanoyl,

50

iii) benzoyl,

iv) phenyl,

v) halophenyl,

vi) phenyl-C₁₋₃alkyl, either unsubstituted or substituted with one or more of halogen, C₁₋₄alkoxy, C₁₋₄alkyl or halo-C₁₋₄alkyl,

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vii) C₁₋₉alkyl,

viii) cinnamyl,

ix) halo-C₁₋₄alkyl,

x) allyl,

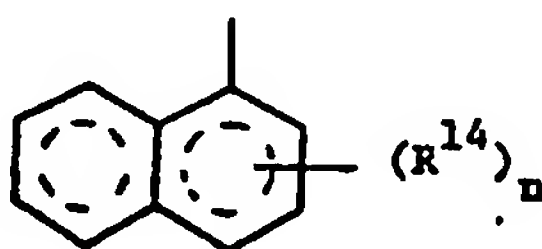
xi) C₃₋₆cycloalkyl-C₁₋₃alkyl, or

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xii) adamantyl-C₁₋₃alkyl;

3)

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0 142 146

wherein n is 0—2 and R¹⁴ is halo or C₁₋₄ alkyl, which comprises treating a compound of structural formula:



wherein R¹⁶ is C₁₋₄alkyl, with an oxidizing agent to produce the compound of structural formula:

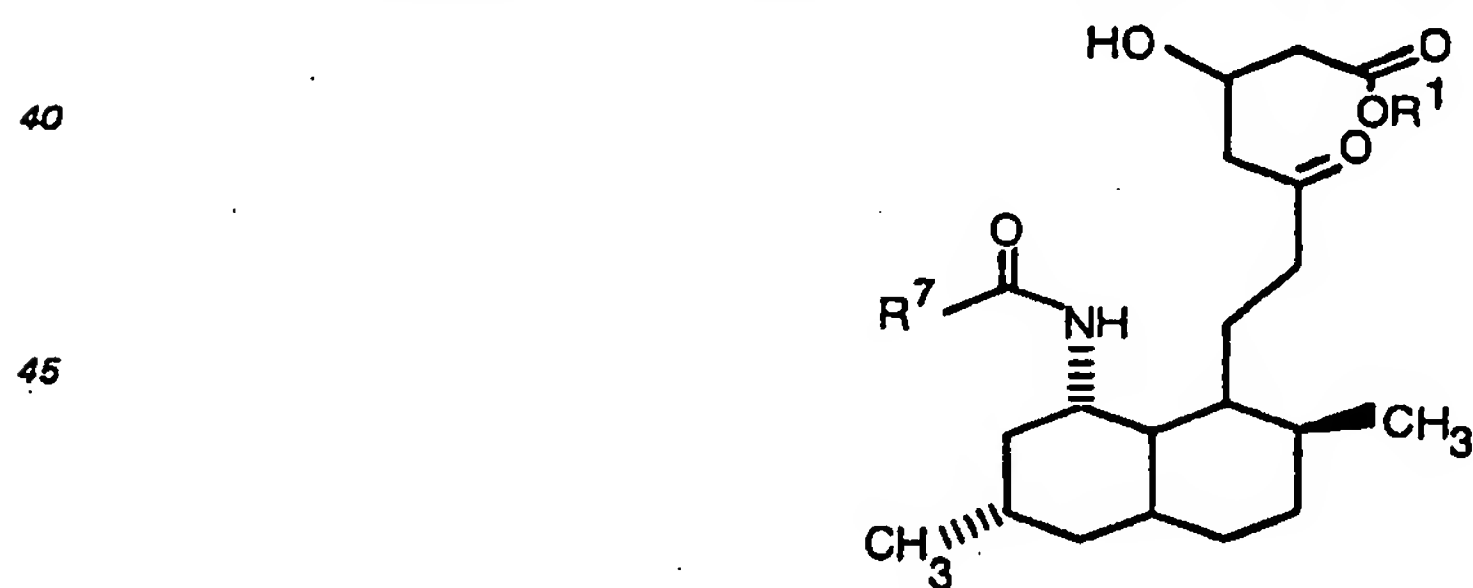


followed by desilylation to produce the compound of structural formula:

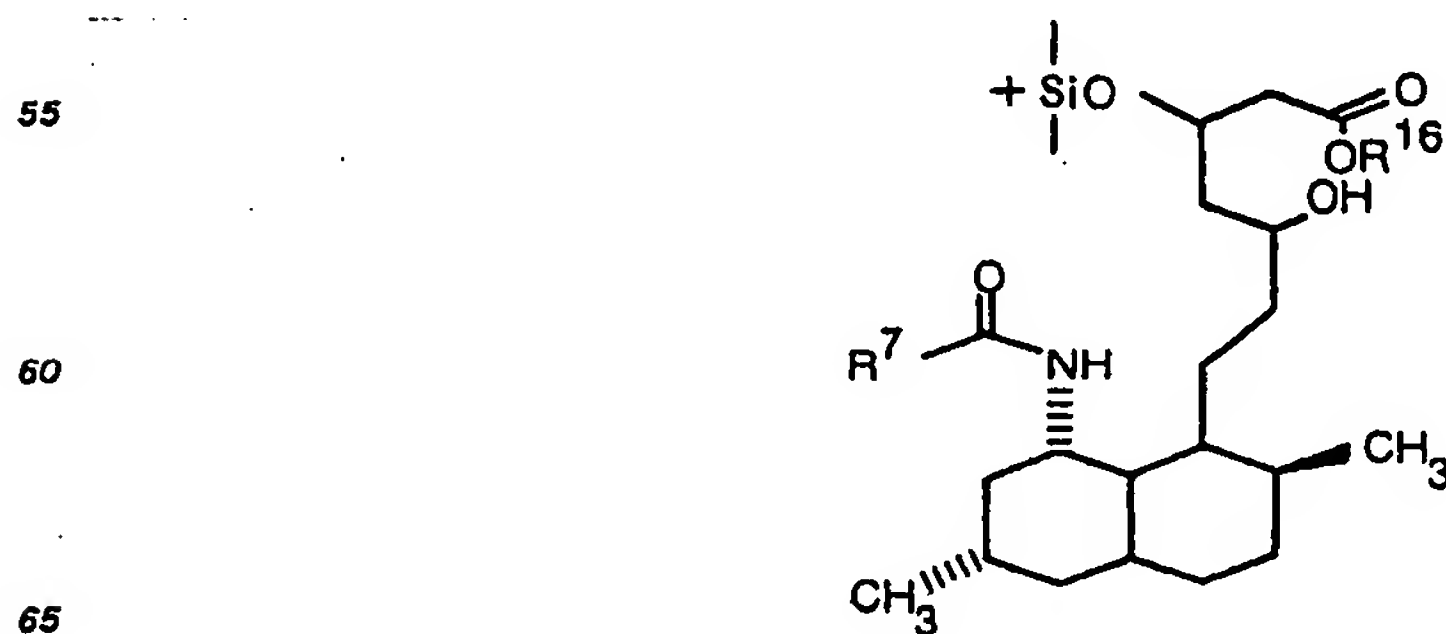


35 followed by treatment with alkali to produce the product wherein R¹⁶ is an alkali metal cation, followed by acidification to produce the compound wherein R¹⁶ is a hydrogen ion.

2. A process for the preparation of a compound of structural formula

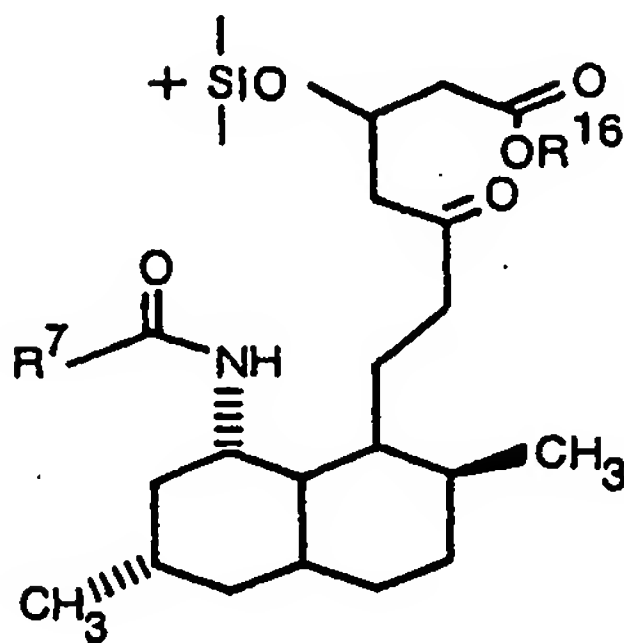


50 wherein R¹ is hydrogen, an alkali metal cation or an ammonium cation and wherein R⁷ is 4-fluorobenzoyl, 4-tert-butylbenzoyl or 4-fluorophenylacetyl, which comprises treating as compound of structural formula:

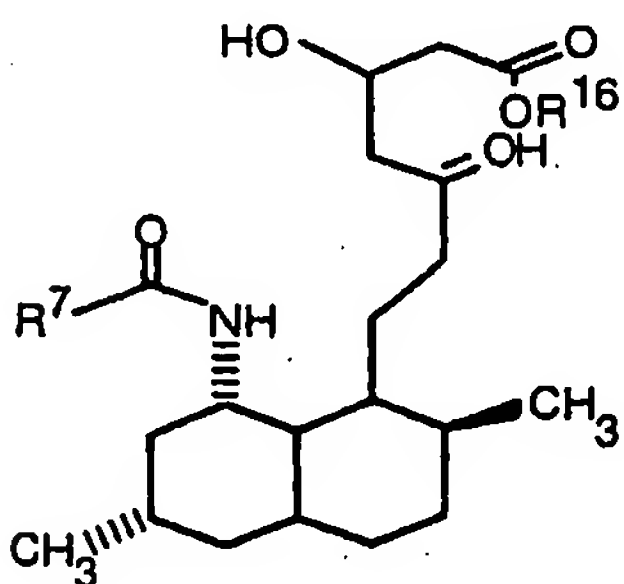


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wherein R^{16} is C_{1-4} alkyl, with an oxidizing agent to produce the compound of structural formula:



followed by desilylation to produce the compound of structural formula:



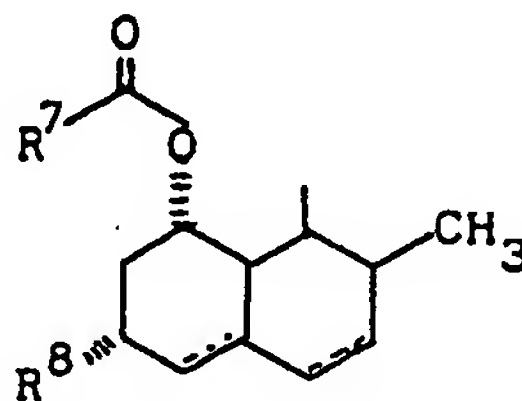
followed by treatment with alkali to produce the product wherein R^{16} is an alkali metal cation, followed by acidification to produce the compound wherein R^{16} is a hydrogen ion.

3. The process of Claim 1 wherein:

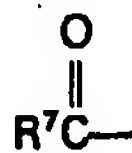
R^1 is hydrogen, an alkali metal cation or an ammonium cation;

E is $-CH=CH-$ or $-CH_2CH_2-$; and

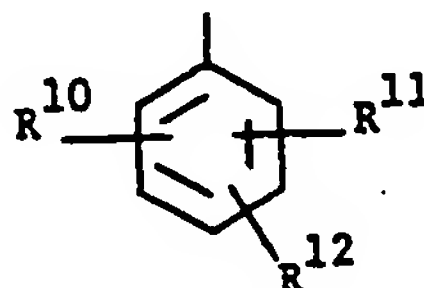
Z is



wherein



is 2(S)-methylbutyryl or 2,2-dimethylbutyryl;



wherein R^{10} , R^{11} and R^{12} are independently

a) halogen,

b) C_{1-4} alkyl,

c) halo- C_{1-4} alkyl,

d) phenyl with 1 to 3 substituents selected from halo, C_{1-4} alkyl or C_{1-4} alkoxy,

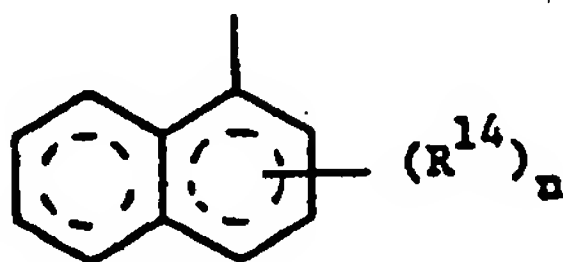
e) OR^{13} , wherein R^{13} is

i) phenyl,

- ii) halophenyl, or
 iii) phenyl-C₁₋₃ alkyl, either unsubstituted or substituted with one or more of halogen, C₁₋₄ alkoxy, C₁₋₄ alkyl or halo-C₁₋₄ alkyl; or

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3)



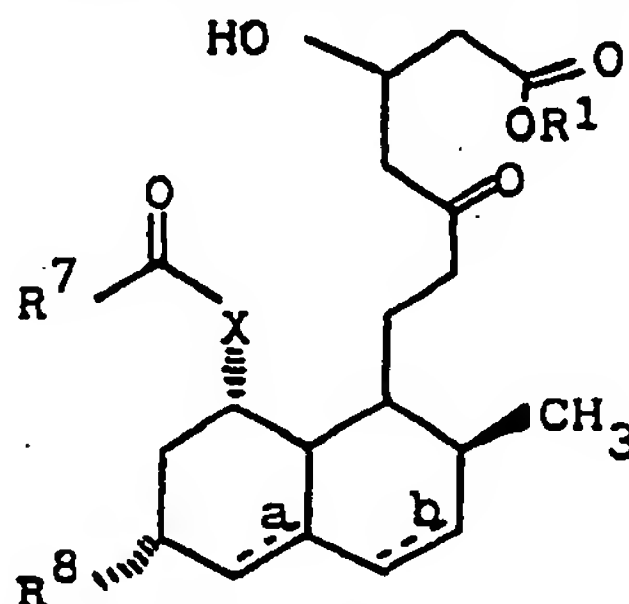
10 wherein n is 0, 1 or 2, and R¹⁴ is methyl, and the ring system is naphthalene, or 5,6,7,8-tetrahydronaphthalene.

4. The process of Claim 1 for the preparation of a compound selected from:

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wherein R¹ is hydrogen, an alkali metal cation or an ammonium cation and wherein R⁷CO—, R⁸, X, a and b have the following meanings:

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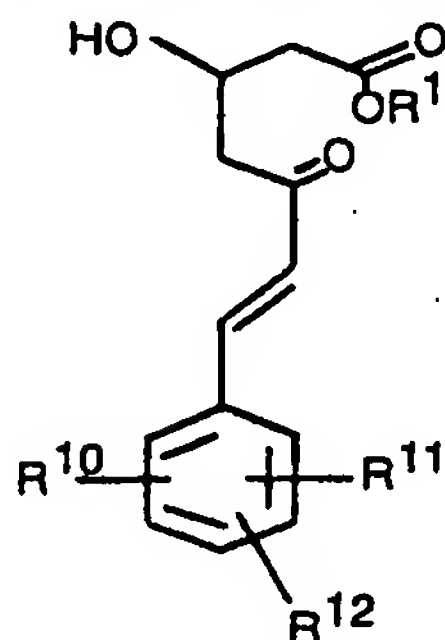
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$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^7\text{C}- \end{array}$	R ⁸	X	a*	b
2(S)-methylbutyryl	—CH ₃	O	single	double
2(S)-methylbutyryl	—CH ₃	O	single	single
2(R)-methylbutyryl	—CH ₃	O	double	double
2,2-dimethylbutyryl	—CH ₃	O	double	double
2,2-dimethylbutyryl	—CH ₃	O	single	double
2,2-dimethylbutyryl	—CH ₃	O	single	single
acetyl	—CH ₃	O	double	double
2(S)-methylbutyryl	H	O	double	double
2(S)-methylbutyryl	H	O	single	single
2,2-dimethylbutyryl	H	O	double	double
2,2-dimethylbutyryl	H	O	single	single
2,2-dimethylbutyryl	—CH ₃	NH	single	single
2-methyl-2-ethylbutyryl	—CH ₃	NH	single	single
2-methylbutyryl	—CH ₃	NH	single	single
acetyl	—CH ₃	NH	double	double
acetyl	—CH ₃	NCH ₃	single	single
2,2-dimethylbutyryl	—CH ₃	NCH ₃	single	single
2,2-dimethylbutyryl	—CH ₃	NH	double	double

* When a = single bond, the rings are *trans*-fused.

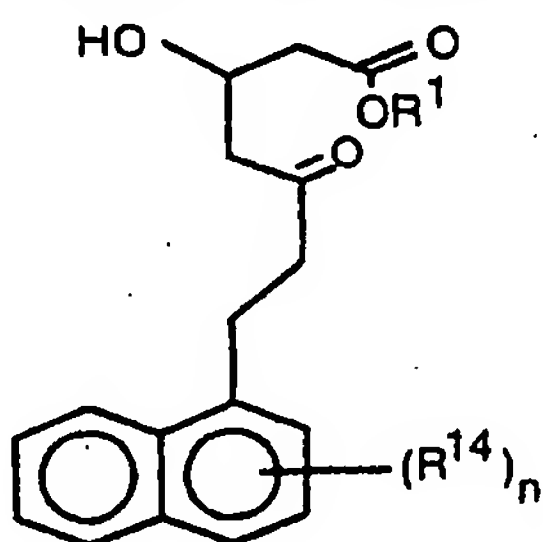
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5. The process of Claim 3 for the preparation of a compound selected from:



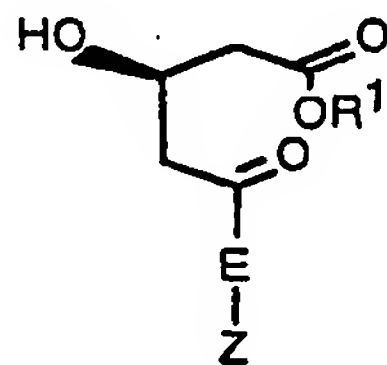
	R ¹⁰	R ¹¹	R ¹²
5	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-methyl
10	6-(4-fluorophenyl)-	2-chloro	4-chloro
15	6-(4-chlorophenyl)-	2-chloro	4-chloro
20	6-(3,4-dichlorophenyl)	2-chloro	4-chloro
25	6-(4-fluoro-3-methylphenyl)	2-chloro	4-chloro
30	6-(3,4-dichlorophenyl)	2-methyl	4-methyl
35	6-(3,5-dimethylphenyl)-	2-chloro	4-chloro
40	6-(3,4-dichlorophenyl)-	2-methyl	5-methyl
	6-(4-fluorophenyl)	2-methyl	4-methyl
	6-(4-fluoro-3-methylphenyl)-	2-methyl	4-chloro
	6-(4-fluorobenzoyloxy)	2-chloro	4-chloro
	6-(4-fluoro-3-methylphenyl)-	2-chloro	4-methyl

6. The process of claim 3 for the preparation of a compound selected from:



n	R ¹⁴	
1	2-methyl	naphthyl
0	—	naphthyl
2	2,6-dimethyl	naphthyl
1	2-methyl	5,6,7,8-tetrahydronaphthyl

7. A process for the preparation of a compound of formula



wherein:

R¹ is

- 1) hydrogen,
- 2) C₁₋₄alkyl,
- 3) 2,3-dihydroxypropyl,
- 4) alkali metal cation, or
- 5) ammonium of formula

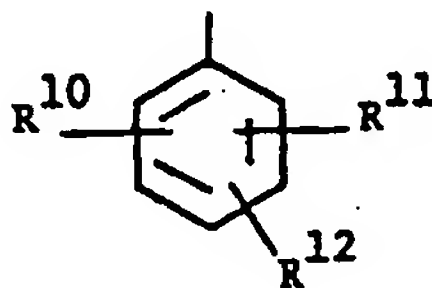


wherein R³, R⁴, R⁵ and R⁶ are independently hydrogen or C₁₋₄alkyl or two of R⁴, R⁵ and R⁶ are joined together to form a 5- or 6-membered heterocycle with the nitrogen to which they are attached;

E is —CH₂CH₂, or —(CH₂)₃—; and

Z is

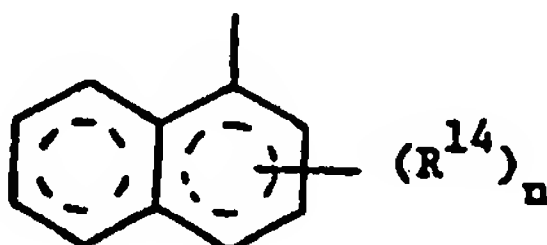
1)



wherein R¹⁰, R¹¹ and R¹² are independently

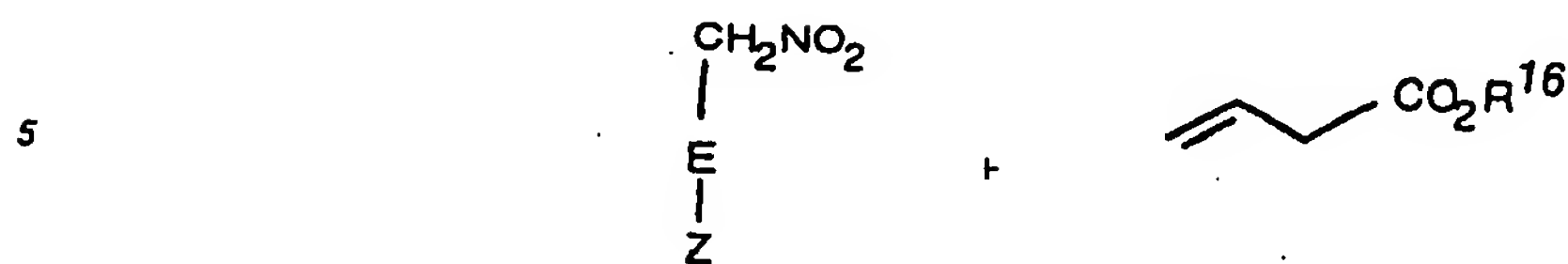
- a) hydrogen,
- b) halogen, such as bromo, chloro or fluoro,
- c) C₁₋₄alkyl,
- d) halo-C₁₋₄alkyl,
- e) phenyl either unsubstituted or substituted with one or more of
 - i) C₁₋₄alkoxy,
 - ii) C₁₋₄alkyl,
 - iii) C₂₋₈alkanoyloxy,
 - iv) halo-C₁₋₄alkyl, or
 - v) halo,
- f) OR¹³ wherein R¹³ is
 - i) hydrogen,
 - ii) C₂₋₈alkanoyl,
 - iii) benzoyl,
 - iv) phenyl,
 - v) halophenyl,
 - vi) phenyl-C₁₋₃alkyl, either unsubstituted or substituted with one or more of halogen, C₁₋₄alkoxy, C₁₋₄alkyl or halo-C₁₋₄alkyl,
 - vii) C₁₋₈alkyl,
 - viii) cinnamyl,
 - ix) halo-C₁₋₄alkyl,
 - x) allyl,
 - xi) C₃₋₆cycloalkyl-C₁₋₃alkyl, or
 - xii) adamantyl-C₁₋₃alkyl;

2)

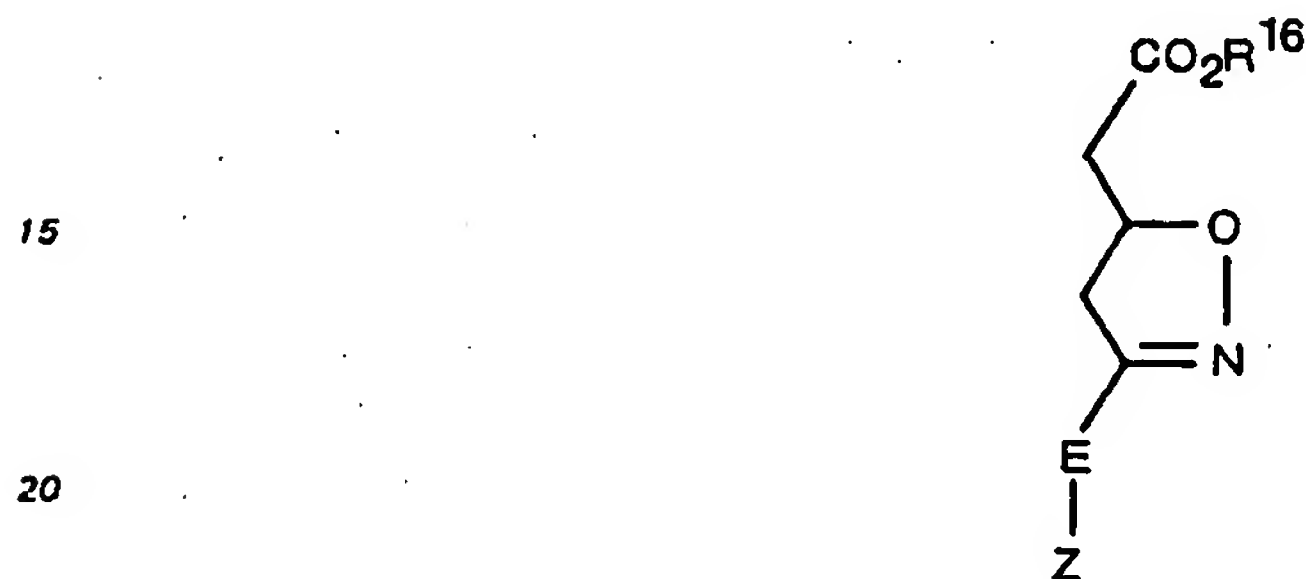


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wherein n is 0—2, and R¹⁴ is halo, or C₁₋₄ alkyl which comprises treating the compounds



10 to produce the compound of structural formula:



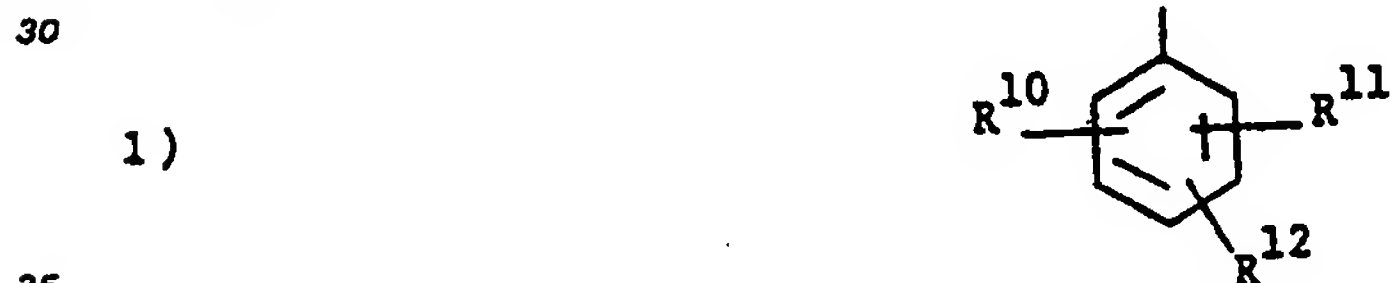
followed by catalytic reduction to produce the desired compound wherein R¹ is R¹⁶; followed by treatment with alkali to produce the product wherein R¹ is an alkali metal cation, followed by acidification to produce the compound wherein R¹ is a hydrogen ion.

8. The process of Claim 7 wherein:

R¹ is hydrogen, an alkali metal cation or an ammonium cation;

E is —CH₂CH₂—; and

Z is



wherein R¹⁰, R¹¹ and R¹² are independently

a) halogen,

b) C₁₋₄alkyl,

c) halo-C₁₋₄alkyl,

d) phenyl with 1 to 3 substituents selected from halo, C₁₋₄alkyl or C₁₋₄alkoxy,

e) OR¹³, wherein R¹³ is

i) phenyl,

ii) halophenyl, or

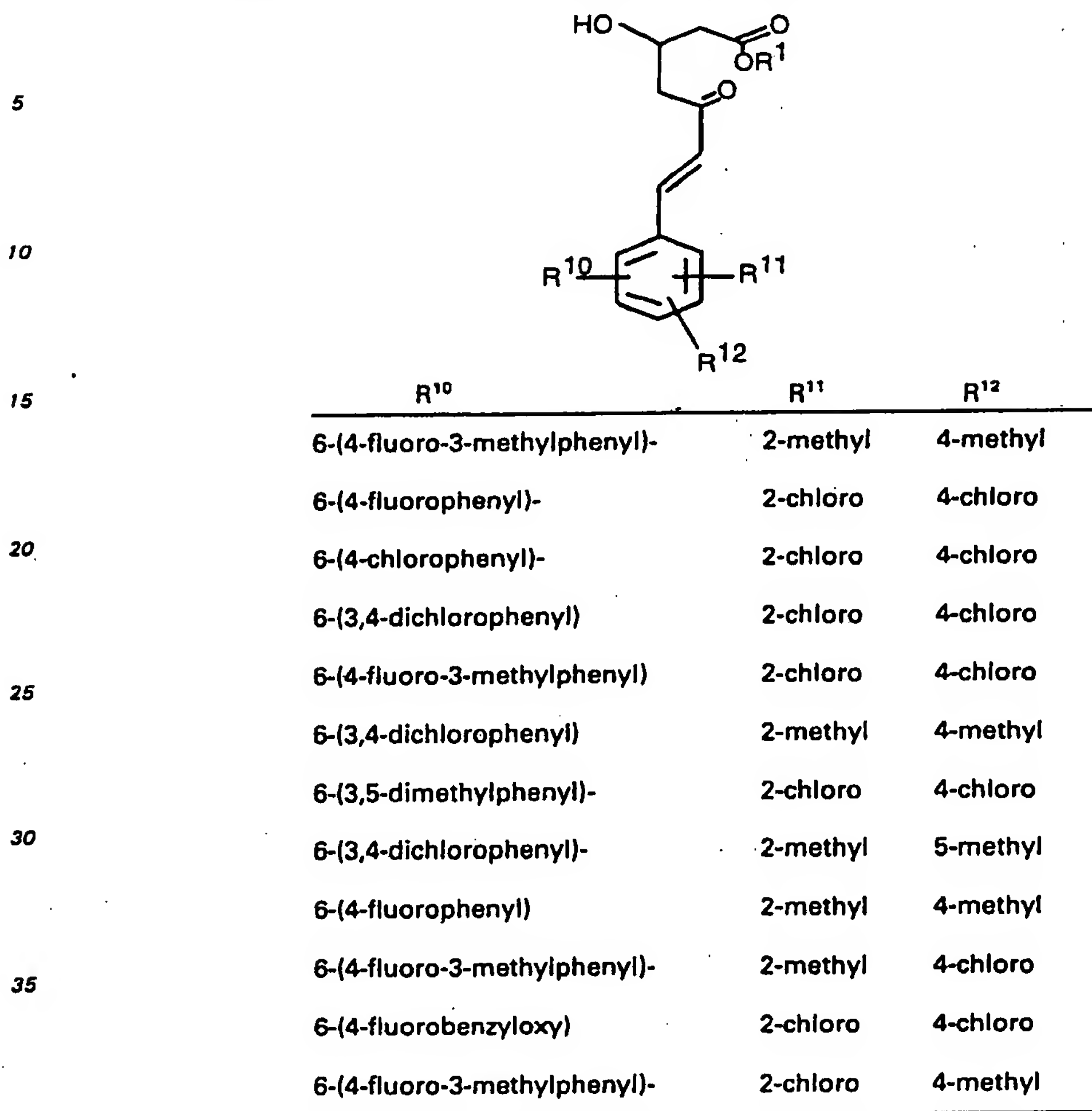
iii) phenyl-C₁₋₃ alkyl, either unsubstituted or substituted with one or more of halogen, C₁₋₄ alkoxy,

C₁₋₄ alkyl, or halo-C₁₋₄ alkyl; or

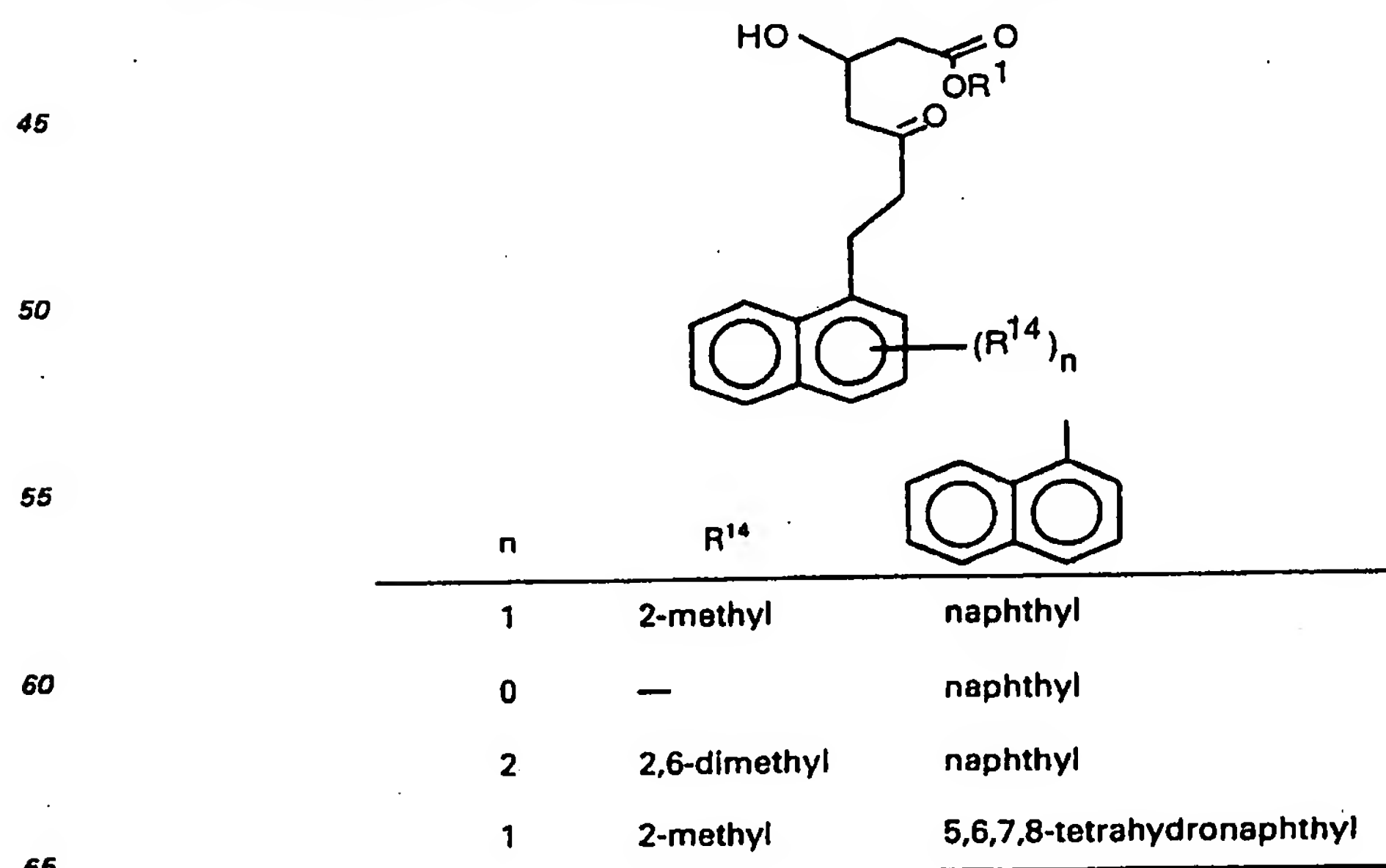


wherein n is 0, 1, or 2, and R¹⁴ is methyl and the ring system is naphthalene or 5,6,7,8-tetrahydronaphthalene.

9. The process of Claim 8 for preparation of a compound selected from:



10. The process of Claim 8 for the preparation of a compound selected from:



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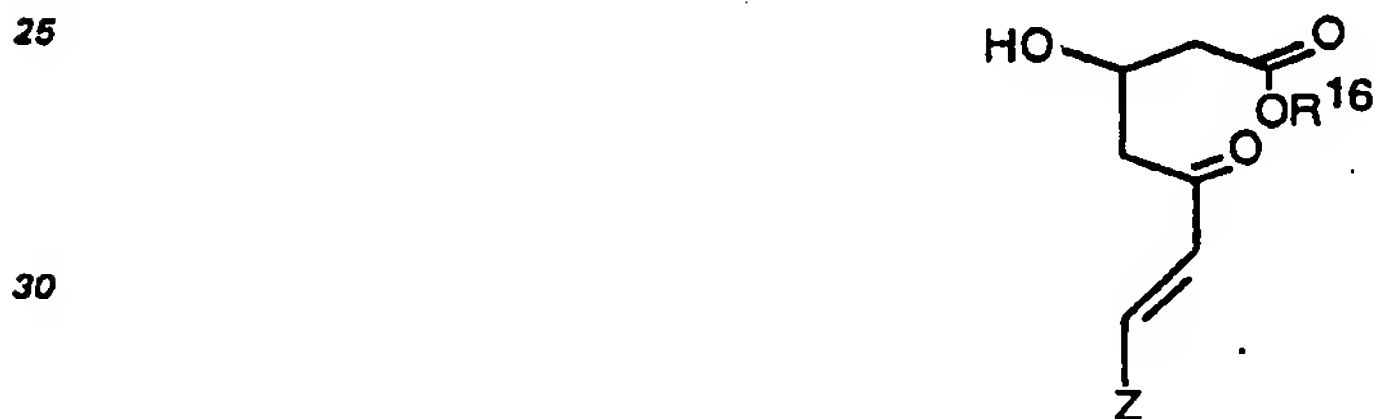
11. A process for the preparation of a compound of structural formula:



wherein Z is as defined in Claim 1, which comprises treating a compound of structural formula:



with activated manganese dioxide to produce the compound of structural formula:



followed by treatment with tri-*n*-butyltin hydride and tetrakis (triphenylphosphine)palladium (O).

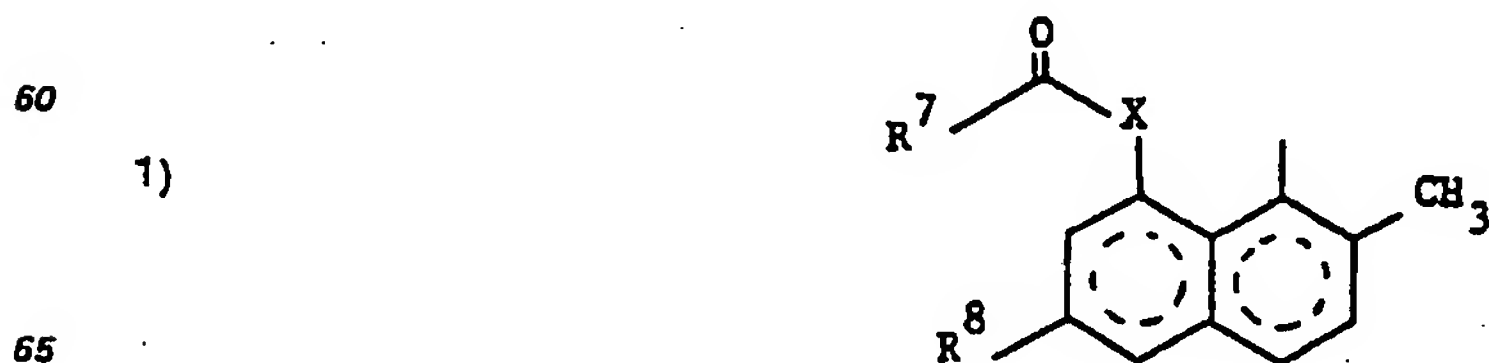
35 Patentansprüche für die Vertragsstaaten: BE CH DE FE GB IT LI LU NL SE

1. Eine Verbindung der Strukturformel:



worin:

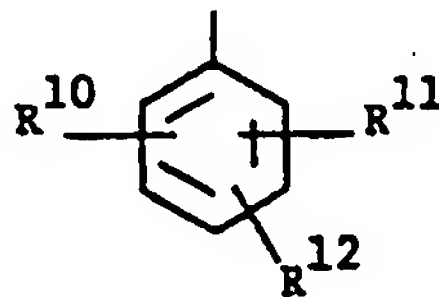
- 50
- R¹) Wasserstoff,
 - 2) C₁₋₄-Alkyl,
 - 3) 2,3-Dihydroxypropyl,
 - 4) ein Alkalimetallkation, oder
 - 5) ein Ammoniumkation der Formel N⁺R³R⁴R⁵R⁶ ist,
- wobei R³, R⁴, R⁵ und R⁶ unabhängig voneinander Wasserstoff oder C₁₋₄-Alkyl sind, oder zwei Reste von R³, R⁴, R⁵ und R⁶ miteinander unter Bildung eines 5- oder 6-gliedrigen Heterocyclus mit dem Stickstoff, an den sie gebunden sind, verbunden sind;
- 55 E —CH₂CH₂—, —CH=CH— oder —(CH₂)₃— ist; und
- Z



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wobei die strichlierten Linien alle möglichen Oxydationszustände des bicyclischen Systems bedeuten, X —O— oder =NR⁹ ist, wobei R⁹ Wasserstoff oder C₁₋₃-Alkyl ist; R⁷ C₂₋₈-Alkyl ist; und R⁸ Wasserstoff oder —CH₃ ist;

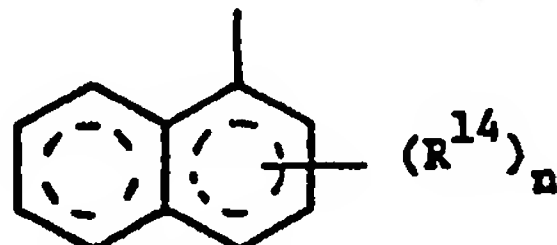
2)



wobei R¹⁰, R¹¹ und R¹² unabhängig voneinander

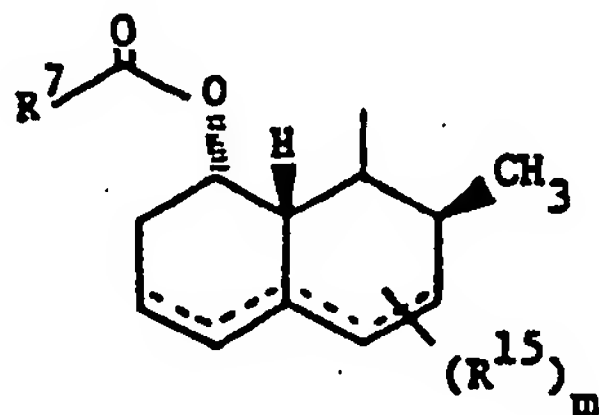
- a) Wasserstoff,
- b) Halogen, wie Brom, Chlor oder Fluor,
- c) C₁₋₄-Alkyl,
- d) Halogen-C₁₋₄-Alkyl,
- e) Phenyl, das entweder unsubstituiert oder durch einen oder mehrere der Substituenten
 - i) C₁₋₄-Alkoxy,
 - ii) C₁₋₄-Alkyl,
 - iii) C₂₋₈-Alkanoyloxy,
 - iv) Halogen-C₁₋₄-Alkyl oder
 - v) Halogen, substituiert ist, oder
- f) OR¹³, wobei R¹³
 - i) Wasserstoff,
 - ii) C₂₋₈-Alkanoyl,
 - iii) Benzoyl,
 - iv) Phenyl,
 - v) Halogenphenyl,
 - vi) Phenyl-C₁₋₃-alkyl, das entweder unsubstituiert oder durch einen oder mehrere Halogen-C₁₋₄-Alkoxy-, C₁₋₄-Alkyl- oder Halogen-C₁₋₄-Alkylreste substituiert ist,
 - vii) C₁₋₉-Alkyl,
 - viii) Zinnamyl,
 - ix) Halogen-C₁₋₄-alkyl,
 - x) Allyl,
 - xi) C₃₋₈-Cycloalkyl-C₁₋₃-alkyl, oder
 - xii) Adamantyl-C₁₋₃-alkyl ist; sind,

3)



wobei n 0—2 ist, und R¹⁴ Halogen oder C₁₋₄-Alkyl ist; und

4)

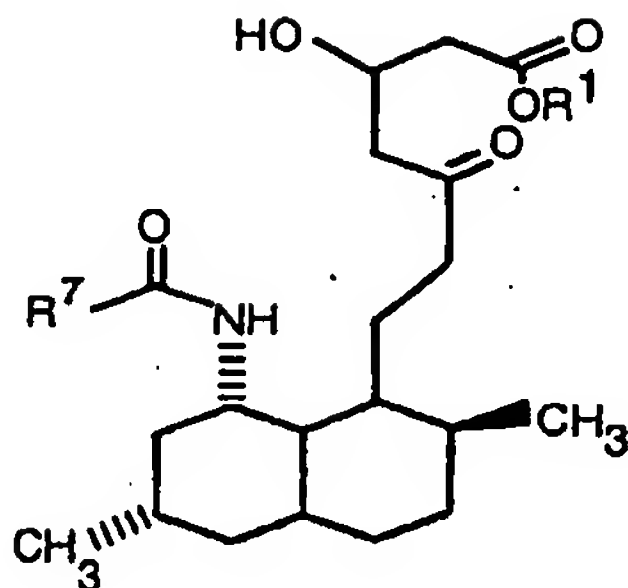


wobei die strichlierten Linien mögliche Doppelbindungen bedeuten und 0, 1 oder 2 Doppelbindungen vorliegen, ist;

m 1, 2 oder 3 bedeutet; und

- R¹⁵ 1) Methyl,
- 2) Hydroxy,
- 3) C₁₋₄-Alkoxy,
- 4) Oxo oder
- 5) Halogen ist.

2. Eine Verbindung der Strukturformel

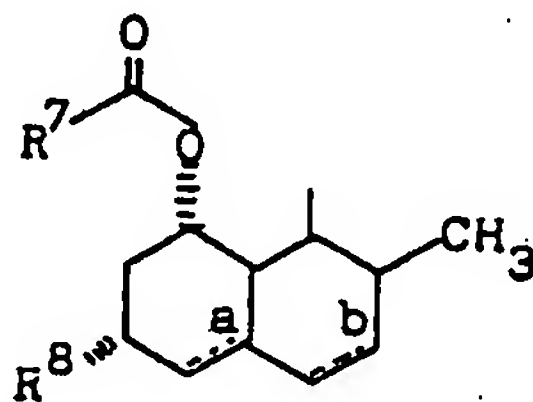


15 worin R^1 Wasserstoff, ein Alkalimetallkation oder ein Ammoniumkation ist, und worin R^7 4-Fluorbenzoyl, 4-tert.-Butylbenzoyl oder 4-Fluorphenylacetyl ist.

3. Die Verbindung von Anspruch 1, worin
 R^1 Wasserstoff, ein Alkalimetallkation oder ein Ammoniumkation ist;

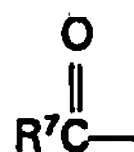
E $-\text{CH}=\text{CH}-$ oder $-\text{CH}_2\text{CH}_2-$ ist; und

Z

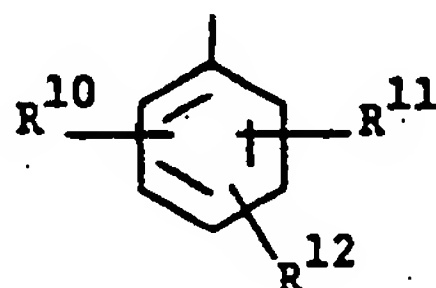


1)

wobei



2(S)-Methylbutyryl oder 2,2-Dimethylbutyryl ist;



wobei R^{10} , R^{11} und R^{12} unabhängig voneinander

a) Halogen,

b) C_{1-4} -Alkyl,

c) Halogen- C_{1-4} -alkyl,

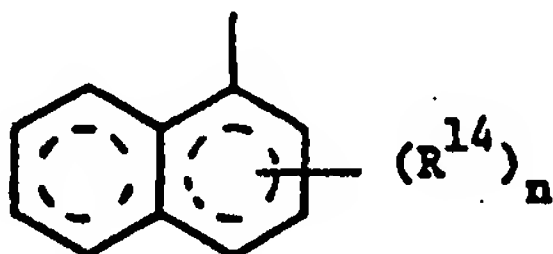
d) Phenyl mit 1 bis 3 Substituenten, ausgewählt aus Halogen, C_{1-4} -Alkyl oder C_{1-4} -Alkoxy, oder

e) OR^{13} , wobei R^{13}

i) Phenyl,

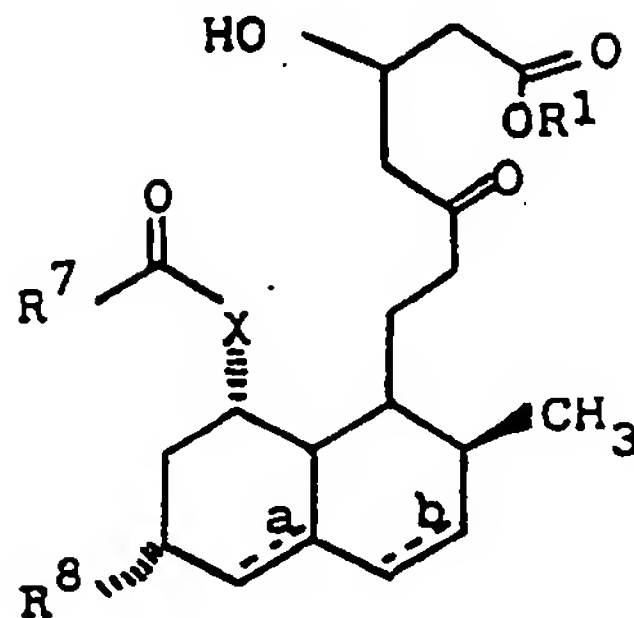
ii) Halogenphenyl oder

iii) Phenyl- C_{1-3} -alkyl ist, das entweder unsubstituiert oder durch einen oder mehrere Halogen-, C_{1-4} -Alkoxy-, C_{1-4} -Alkyl- oder Halogen- C_{1-4} -alkylreste substituierte ist, darstellen; oder



wobei n 0, 1 oder 2 ist, und R^{14} Methyl ist, und das Ringsystem Naphthyl oder 5,6,7,8-Tetrahydronaphthyl ist, bedeutet.

4. Die Verbindung von Anspruch 1, ausgewählt aus:



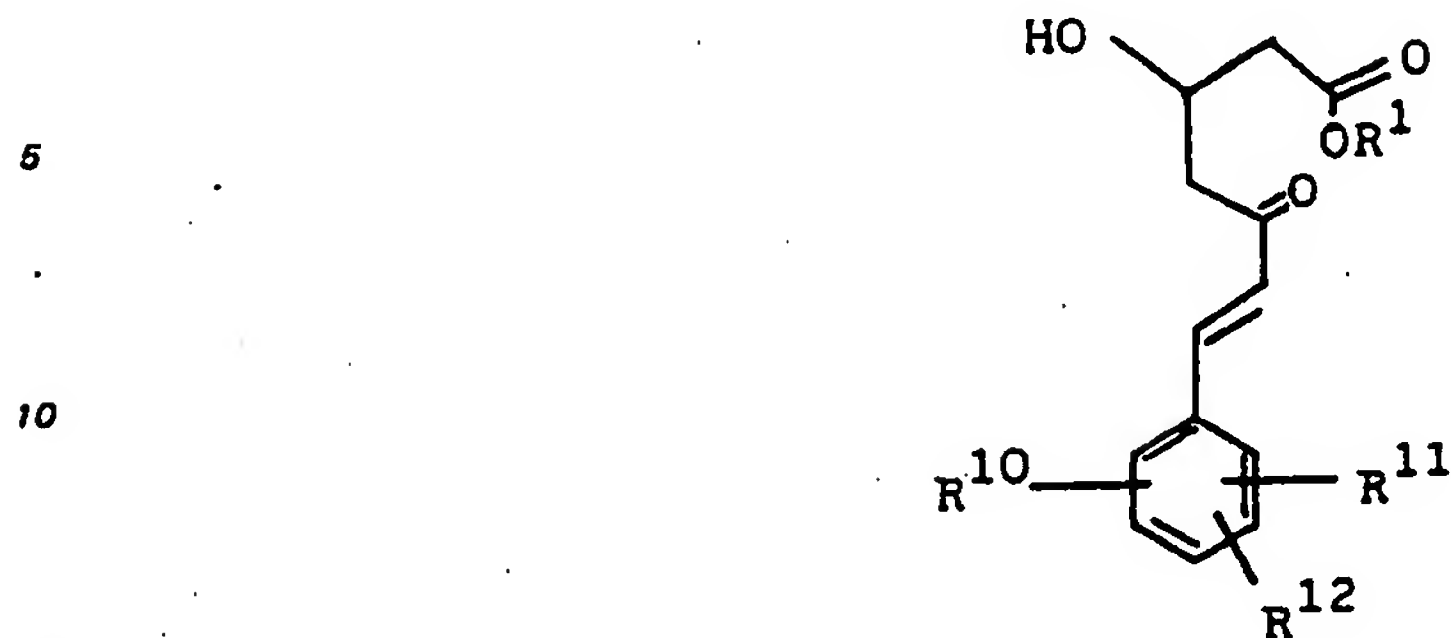
worin R¹ Wasserstoff, ein Alkalimetallkation oder ein Ammoniumkation ist, und worin R⁷CO—, R⁸, X, a und b die folgenden Bedeutungen haben:

	$\begin{matrix} \text{O} \\ \parallel \\ \text{R}^7\text{C}- \end{matrix}$	R ⁸	X	a*	b
	2(S)-Methylbutyryl	-CH ₃	O	Einfachbindung	Doppelbindung
25	2(S)-Methylbutyryl	-CH ₃	O	Einfachbindung	Einfachbindung
	2(R)-Methylbutyryl	-CH ₃	O	Doppelbindung	Doppelbindung
	2,2-Dimethylbutyryl	-CH ₃	O	Doppelbindung	Doppelbindung
	2,2-Dimethylbutyryl	-CH ₃	O	Einfachbindung	Doppelbindung
30	2,2-Dimethylbutyryl	-CH ₃	O	Einfachbindung	Einfachbindung
	Acetyl	-CH ₃	O	Doppelbindung	Doppelbindung
	2(S)-Methylbutyryl	H	O	Doppelbindung	Doppelbindung
35	2(S)-Methylbutyryl	H	O	Einfachbindung	Einfachbindung
	2,2-Dimethylbutyryl	H	O	Doppelbindung	Doppelbindung
	2,2-Dimethylbutyryl	H	O	Einfachbindung	Einfachbindung
40	2,2-Dimethylbutyryl	-CH ₃	NH	Einfachbindung	Einfachbindung
	2-Methyl-2-ethylbutyryl	-CH ₃	NH	Einfachbindung	Einfachbindung
	2-Methylbutyryl	-CH ₃	NH	Einfachbindung	Einfachbindung
45	Acetyl	-CH ₃	NH	Doppelbindung	Doppelbindung
	Acetyl	-CH ₃	NCH ₃	Einfachbindung	Einfachbindung
	2,2-Dimethylbutyryl	-CH ₃	NCH ₃	Einfachbindung	Einfachbindung
50	2,2-Dimethylbutyryl	-CH ₃	NH	Doppelbindung	Doppelbindung

* Falls a eine Einfachbindung ist, sind die Ringe trans-kondensiert.

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5. Die Verbindung von Anspruch 3, ausgewählt aus:



15

R¹⁰	R¹¹	R¹²
6-(4-Fluor-3-methylphenyl)-	2-Methyl	4-Methyl
6-(4-Fluorphenyl)-	2-Chlor	4-Chlor
6-(4-Chlorphenyl)-	2-Chlor	4-Chlor
6-(3,4-Dichlorphenyl)	2-Chlor	4-Chlor
6-(4-Fluor-3-methylphenyl)	2-Chlor	4-Chlor
6-(3,4-Dichlorphenyl)	2-Methyl	4-Methyl
5-(3,5-Dimethylphenyl)-	2-Chlor	4-Chlor
6-(3,4-Dichlorphenyl)-	2-Methyl	5-Methyl
6-(4-Fluorphenyl)	2-Methyl	4-Methyl
6-(4-Fluor-3-methylphenyl)-	2-Methyl	4-Chlor
6-(4-Fluorbenzyloxy)	2-Chlor	4-Chlor
6-(4-Fluor-3-methylphenyl)-	2-Chlor	4-Methyl

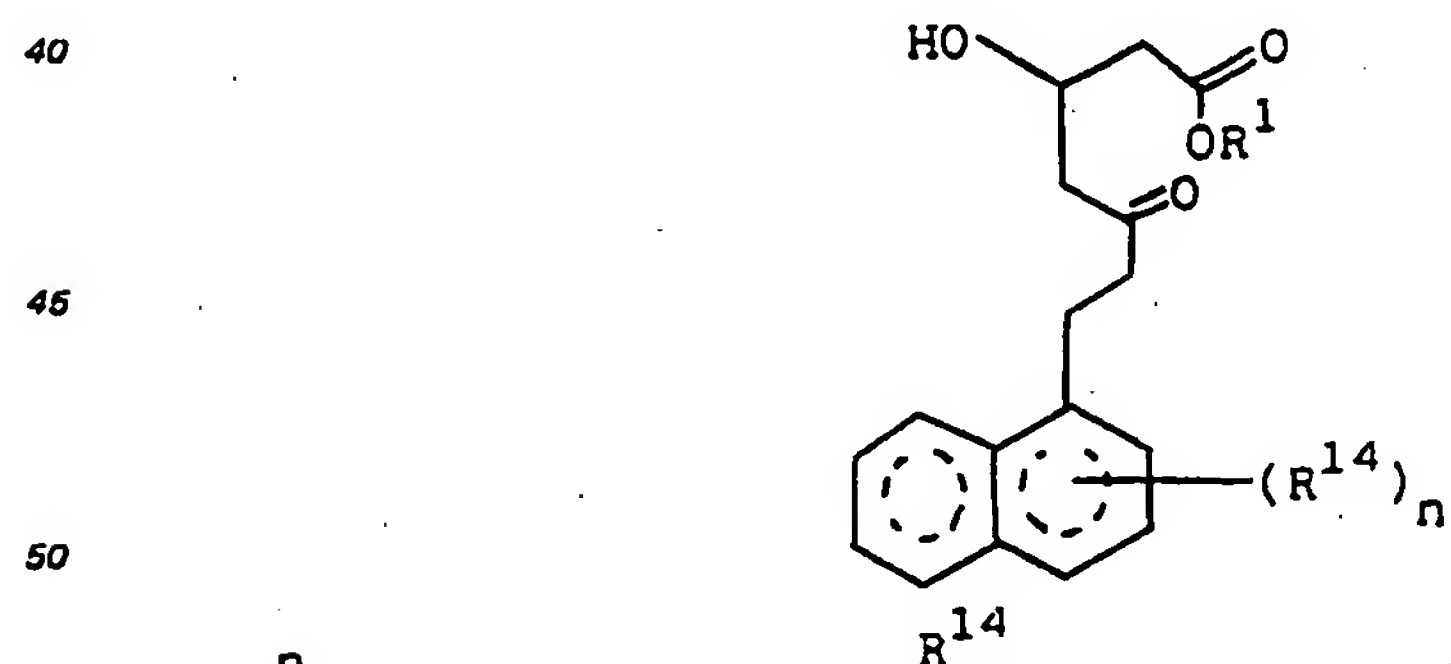
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35

6. Die Verbindung von Anspruch 3, ausgewählt aus:



55

n	R¹⁴	Naphthyl
1	2-Methyl	Naphthyl
0	-	Naphthyl
2	2,6-Dimethyl	Naphthyl
1	2-Methyl	5,6,7,8-Tetrahydro-naphthyl

60

7. Eine antihypercholesterinämische, pharmazeutische Zusammensetzung, enthaltend einen pharmazeutischen Träger und eine antihypercholesterinämisch wirksame Menge einer Verbindung wie in Anspruch 1 oder 2 beansprucht.

8. Die Formulierung von Anspruch 7, wobei die antihypercholesterinämische Verbindung eine in Anspruch 3 beanspruchte Verbindung ist.

9. Die Formulierung von Anspruch 8, wobei die antihypercholesterinämische Verbindung eine in den Ansprüchen 4, 5 oder 6 beanspruchte Verbindung ist.

5 10. Ein Verfahren zur Herstellung einer Verbindung der Strukturformel:



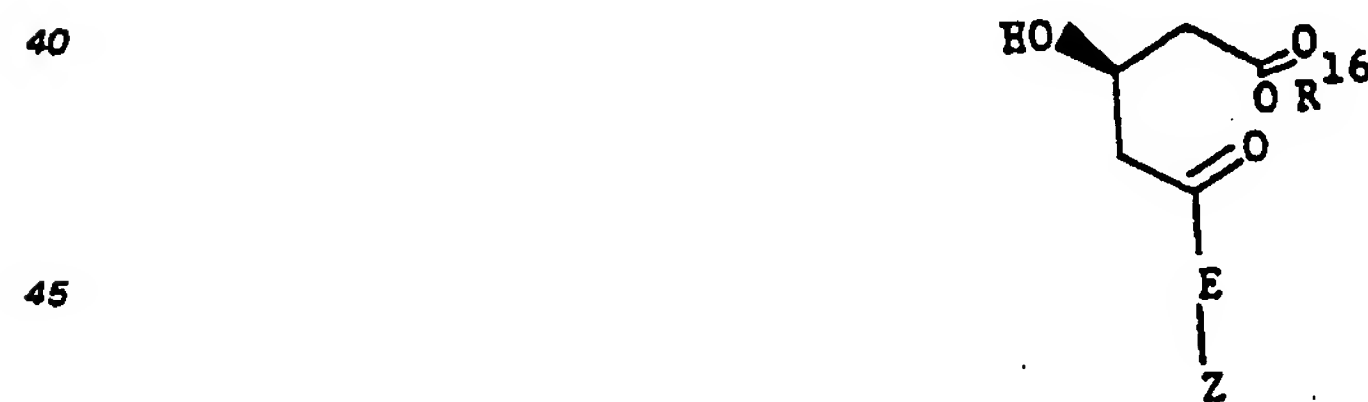
15 worin R¹, E und Z die in Anspruch 1 angegebenen Bedeutungen von R¹, E und Z 1), 2) und 3) haben, welches das Behandeln einer Verbindung der Strukturformel



25 worin R¹⁶ C₁₋₄-Alkyl ist, mit einem Oxydationsmittel unter Bildung der Verbindung der Strukturformel:



gefolgt von der Entsilylierung unter Bildung der Verbindung der Strukturformel:



50 gefolgt von der Behandlung mit Alkali unter Bildung des Produktes, worin R¹⁶ ein Alkalimetallkation ist, gefolgt von der Ansäuerung unter Bildung der Verbindung, worin R¹⁶ ein Wasserstoffion ist, umfaßt.

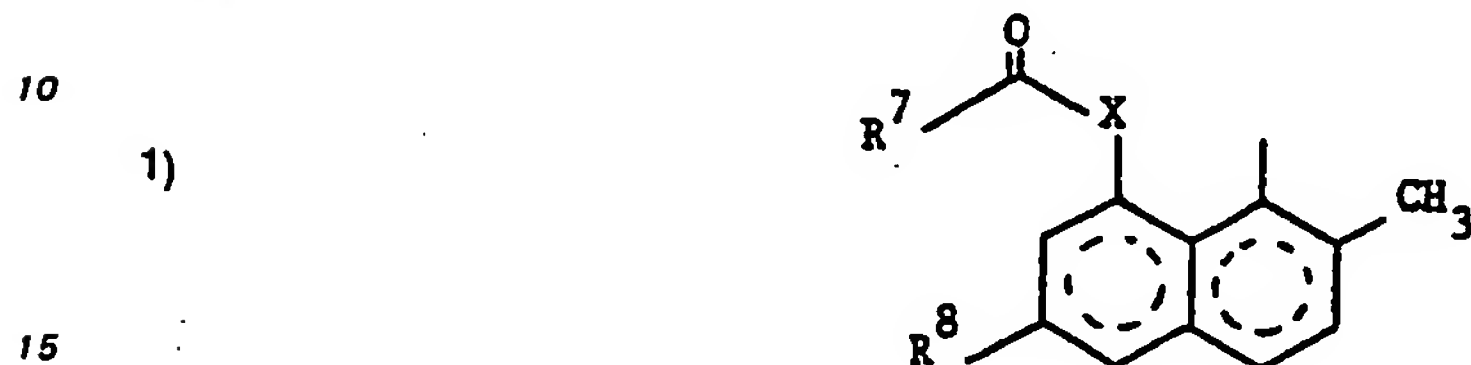
Patentansprüche für den Vertragsstaat: AT

55 1. Eine Verfahren zur Herstellung einer Verbindung der Strukturformel:



65 worin:
R¹ 1) Wasserstoff,
2) C₁₋₄-Alkyl,

- 3) 2,3-Dihydroxypropyl,
 4) ein Alkalimetallkation, oder
 5) ein Ammoniumkation der Formel $N^+R^3R^4R^5R^6$ ist,
 wobei R^3 , R^4 , R^5 und R^6 unabhängig voneinander Wasserstoff oder C_{1-4} -Alkyl sind, oder zwei Reste von R^3 ,
 5 R^4 , R^5 und R^6 miteinander unter Bildung eines 5- oder 6-gliedrigen Heterocyclus mit dem Stickstoff, an den
 sie gebunden sind, verbunden sind;
 $E - CH_2CH_2, -CH=CH-$ oder $-(CH_2)_3-$ ist; und
 Z



- wobei die strichlierten Linien alle möglichen Oxydationszustände des bicyclischen Systems bedeuten, X
 $-O-$ oder $=NR^9$ ist, wobei R^9 Wasserstoff oder C_{1-3} -Alkyl ist;
 R^7 C_{2-8} -Alkyl ist; und
 20 R^8 Wasserstoff oder $-CH_3$ ist;



- wobei R^{10} , R^{11} und R^{12} unabhängig voneinander
 a) Wasserstoff,
 30 b) Halogen, wie Brom, Chlor oder Fluor,
 c) C_{1-4} -Alkyl,
 d) Halogen- C_{1-4} -Alkyl,
 e) Phenyl, das entweder unsubstituiert oder durch einen oder mehrere der Substituenten
 35 i) C_{1-4} -Alkoxy,
 ii) C_{1-4} -Alkyl,
 iii) C_{2-8} -Alkanoyloxy,
 iv) Halogen- C_{1-4} -Alkyl oder
 v) Halogen, substituiert ist, oder
 f) OR^{13} , wobei R^{13}
 40 i) Wasserstoff,
 ii) C_{2-8} -Alkanoyl,
 iii) Benzoyl,
 iv) Phenyl,
 v) Halogenphenyl,
 45 vi) Phenyl- C_{1-3} -alkyl, das entweder unsubstituiert oder durch einen oder mehrere Halogen- C_{1-4} -
 Alkoxy-, C_{1-4} -Alkyl- oder Halogen- C_{1-4} -Alkylreste substituiert ist,
 vii) C_{1-8} -Alkyl,
 viii) Zinnamyl,
 ix) Halogen- C_{1-4} -alkyl,
 50 x) Allyl,
 xi) C_{3-6} -Cycloalkyl- C_{1-3} -alkyl, oder
 xii) Adamantyl- C_{1-3} -alkyl ist, sind; oder



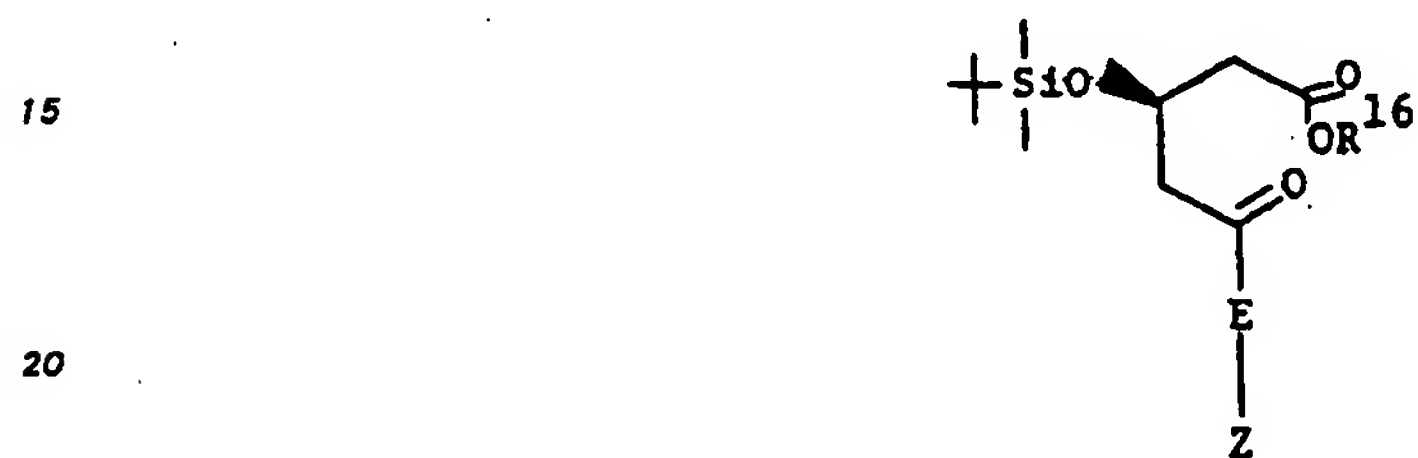
- 60 wobei n 0—2 ist, und R^{14} Halogen oder C_{1-4} -Alkyl ist; bedeutet;

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welches das Behandeln einer Verbindung der Strukturformel



worin R^{16} C_{1-4} -Alkyl ist, mit einem Oxydationsmittel unter Bildung der Verbindung der Strukturformel:



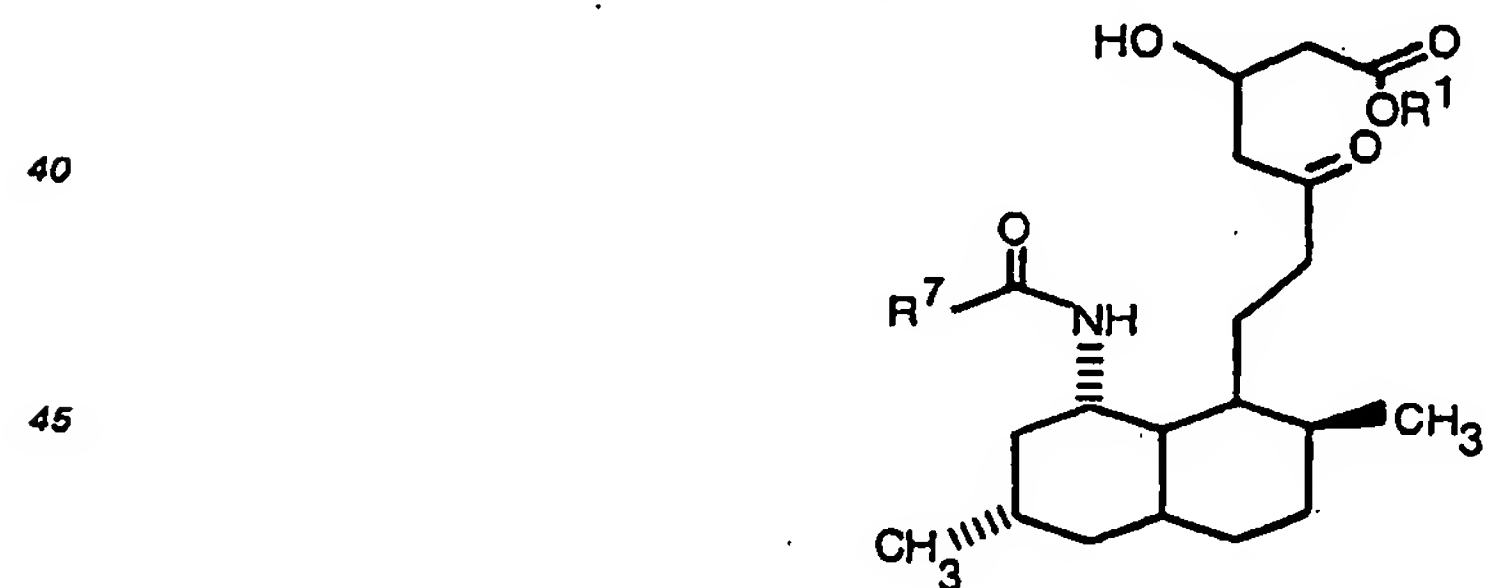
gefolgt von der Entsilylierung unter Bildung der Verbindung der Strukturformel:



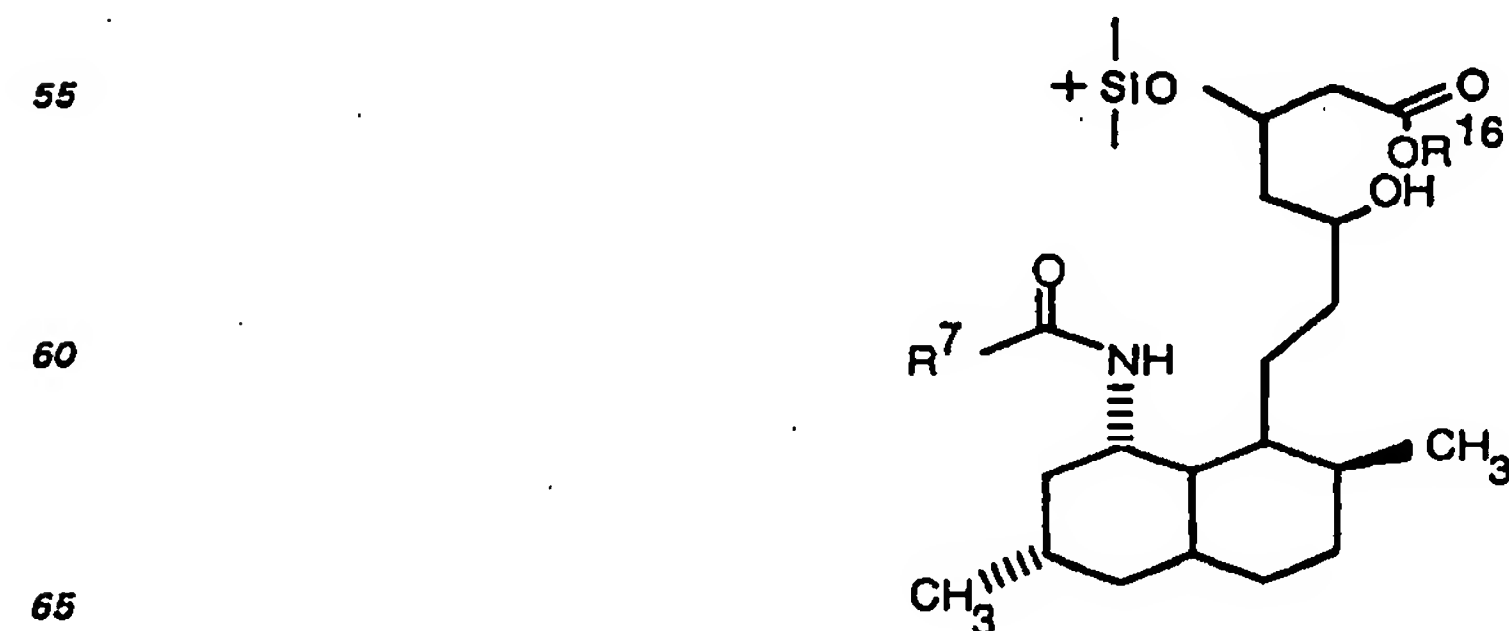
gefolgt von der Behandlung mit Alkali unter Bildung des Produktes, worin R^{16} ein Alkalimetallkation ist, gefolgt von der Ansäuerung unter Bildung der Verbindung, worin R^{16} ein Wasserstoffion ist, umfaßt.

35

2. Ein Verfahren zur Herstellung einer Verbindung der Strukturformel

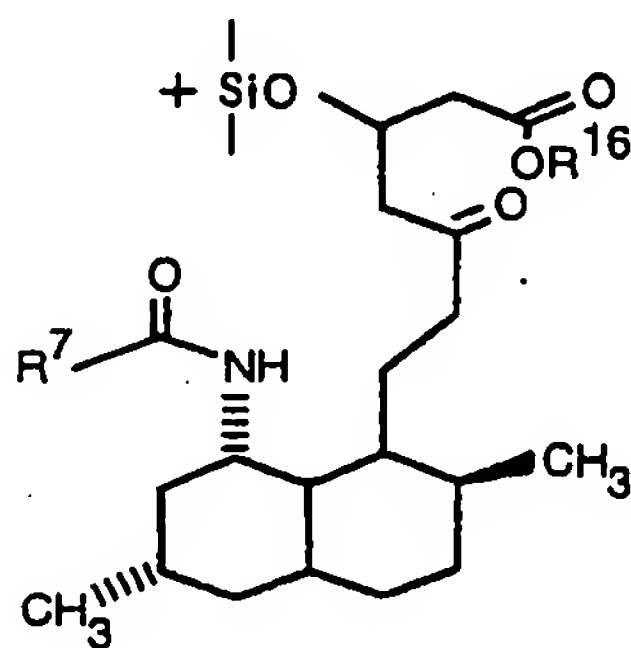


worin R^1 Wasserstoff, ein Alkalimetallkation oder ein Ammoniumkation ist, und worin R^7 4-Fluorbenzoyl, 4-tert.-Butylbenzoyl oder 4-Fluorphenylacetyl ist, welches das Behandeln einer Verbindung der Strukturformel

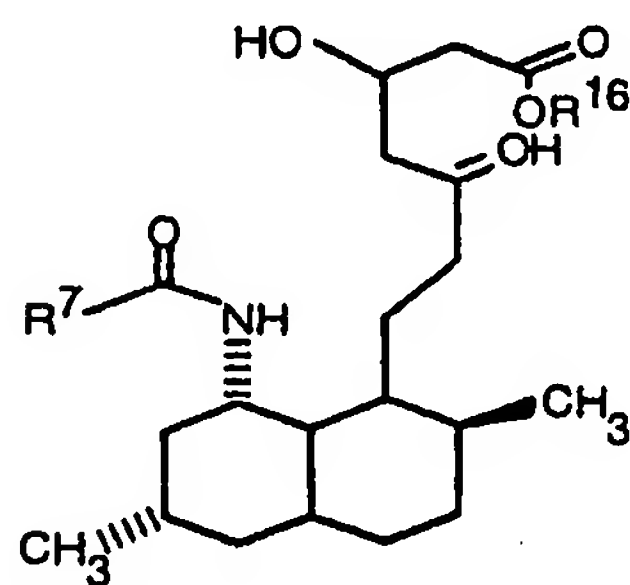


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worin R^{16} C_{1-4} -Alkyl ist, mit einem Oxydationsmittel unter Bildung der Verbindung der Strukturformel:

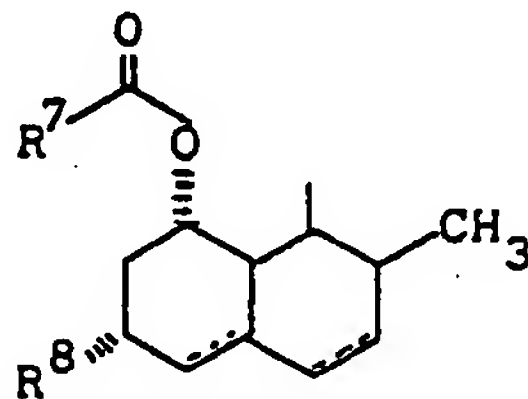


gefolgt von der Entsilylierung unter Bildung der Verbindung der Strukturformel:



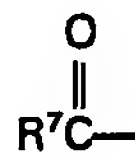
gefolgt von der Behandlung mit Alkali unter Bildung des Produktes, worin R^{16} ein Alkalimetallkation ist, gefolgt von der Ansäuerung unter Bildung der Verbindung, worin R^{16} ein Wasserstoffion ist, umfaßt.

3. Das Verfahren von Anspruch 1, worin
 R^1 Wasserstoff, ein Alkalimetallkation oder ein Ammoniumkation ist;
 E $-\text{CH}=\text{CH}-$ oder $-\text{CH}_2\text{CH}_2-$ ist; und
 Z

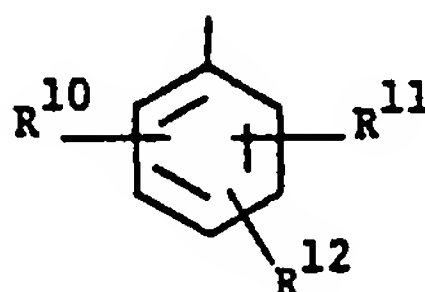


1)

wobei



2(S)-Methylbutyryl oder 2,2-Dimethylbutyryl ist;



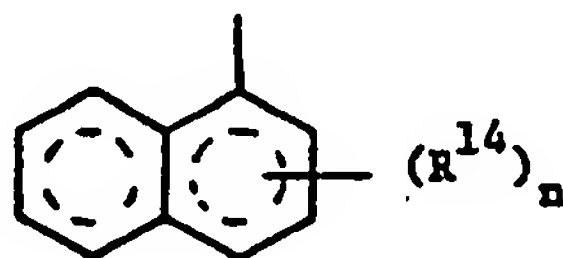
2)

wobei R^{10} , R^{11} und R^{12} unabhängig voneinander

- a) Halogen,
- b) C_{1-4} -Alkyl,
- c) Halogen- C_{1-4} -alkyl,
- d) Phenyl mit 1 bis 3 Substituenten, ausgewählt aus Halogen, C_{1-4} -Alkyl oder C_{1-4} -Alkoxy, oder
- e) OR^{13} , wobei R^{13}
- i) Phenyl,

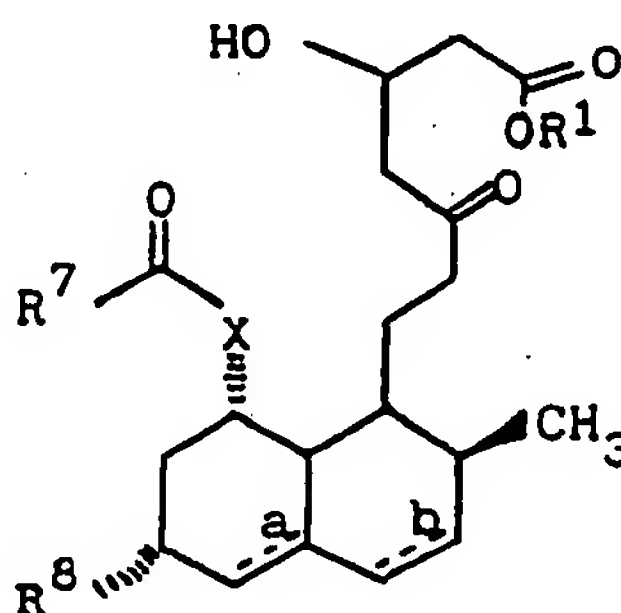
- ii) Halogenphenyl oder
 iii) Phenyl-C₁₋₃-alkyl ist, das entweder unsubstituiert oder durch einen oder mehrere Halogen-, C₁₋₄-Alkoxy-, C₁₋₄-Alkyl- oder Halogen-C₁₋₄-alkylreste substituierte ist, darstellen; oder

3)



wobei n 0, 1 oder 2 ist, und R¹⁴ Methyl ist, und das Ringsystem Naphthyl oder 5,6,7,8-Tetrahydronaphthyl ist, bedeutet.

4. Das Verfahren von Anspruch 1 zur Herstellung einer Verbindung, ausgewählt aus:



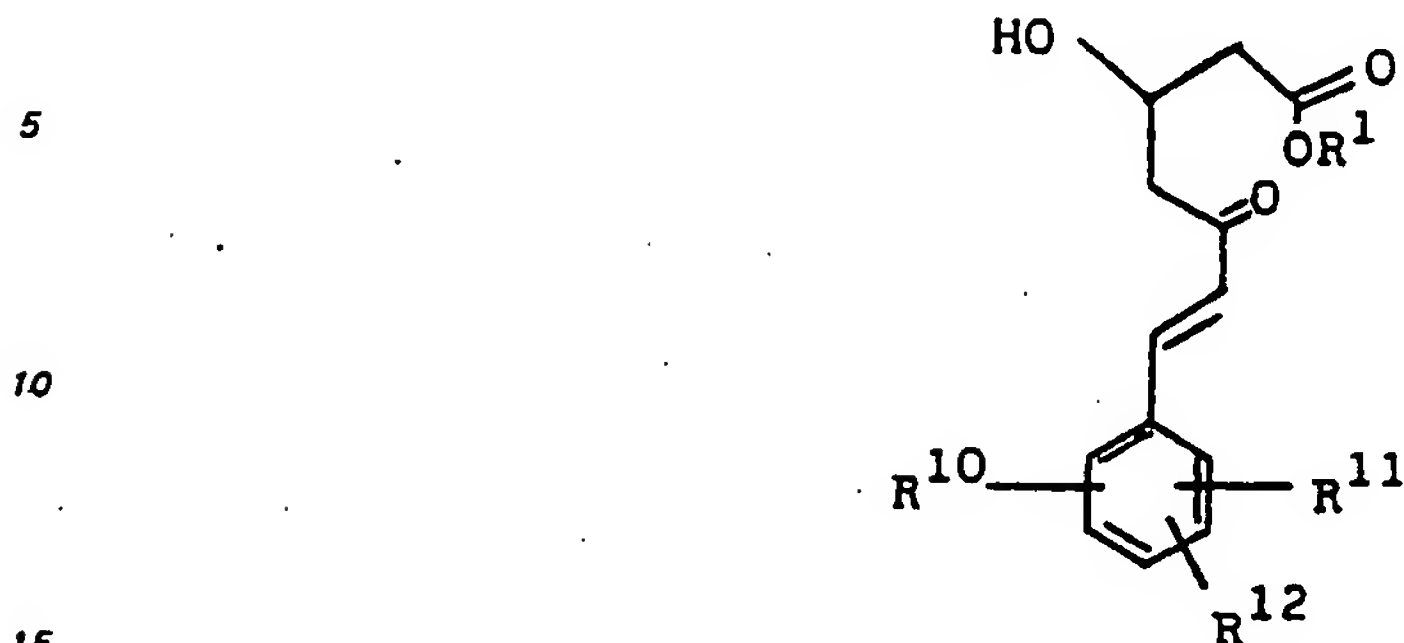
worin R¹ Wasserstoff, ein Alkalimetallkation oder ein Ammoniumkation ist, und worin R⁷CO—, R⁸, X, a und b die folgenden Bedeutungen haben:

	$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^7\text{C}- \end{array}$	R ⁸	X	a*	b
2(S)-Methylbutyryl		-CH ₃	O	Einfachbindung	Doppelbindung
2(S)-Methylbutyryl		-CH ₃	O	Einfachbindung	Einfachbindung
2(R)-Methylbutyryl		-CH ₃	O	Doppelbindung	Doppelbindung
2,2-Dimethylbutyryl		-CH ₃	O	Doppelbindung	Doppelbindung
2,2-Dimethylbutyryl		-CH ₃	O	Einfachbindung	Doppelbindung
2,2-Dimethylbutyryl		-CH ₃	O	Einfachbindung	Einfachbindung
Acetyl		-CH ₃	O	Doppelbindung	Doppelbindung
2(S)-Methylbutyryl		H	O	Doppelbindung	Doppelbindung
2(S)-Methylbutyryl		H	O	Einfachbindung	Einfachbindung
2,2-Dimethylbutyryl		H	O	Doppelbindung	Doppelbindung
2,2-Dimethylbutyryl		H	O	Einfachbindung	Einfachbindung
2,2-Dimethylbutyryl		-CH ₃	NH	Einfachbindung	Einfachbindung
2-Methyl-2-ethylbutyryl		-CH ₃	NH	Einfachbindung	Einfachbindung
2-Methylbutyryl		-CH ₃	NH	Einfachbindung	Einfachbindung
Acetyl		-CH ₃	NH	Doppelbindung	Doppelbindung
Acetyl		-CH ₃	NCH ₃	Einfachbindung	Einfachbindung
2,2-Dimethylbutyryl		-CH ₃	NCH ₃	Einfachbindung	Einfachbindung
2,2-Dimethylbutyryl		-CH ₃	NH	Doppelbindung	Doppelbindung

* Falls a eine Einfachbindung ist, sind die Ringe trans-konfiguriert.

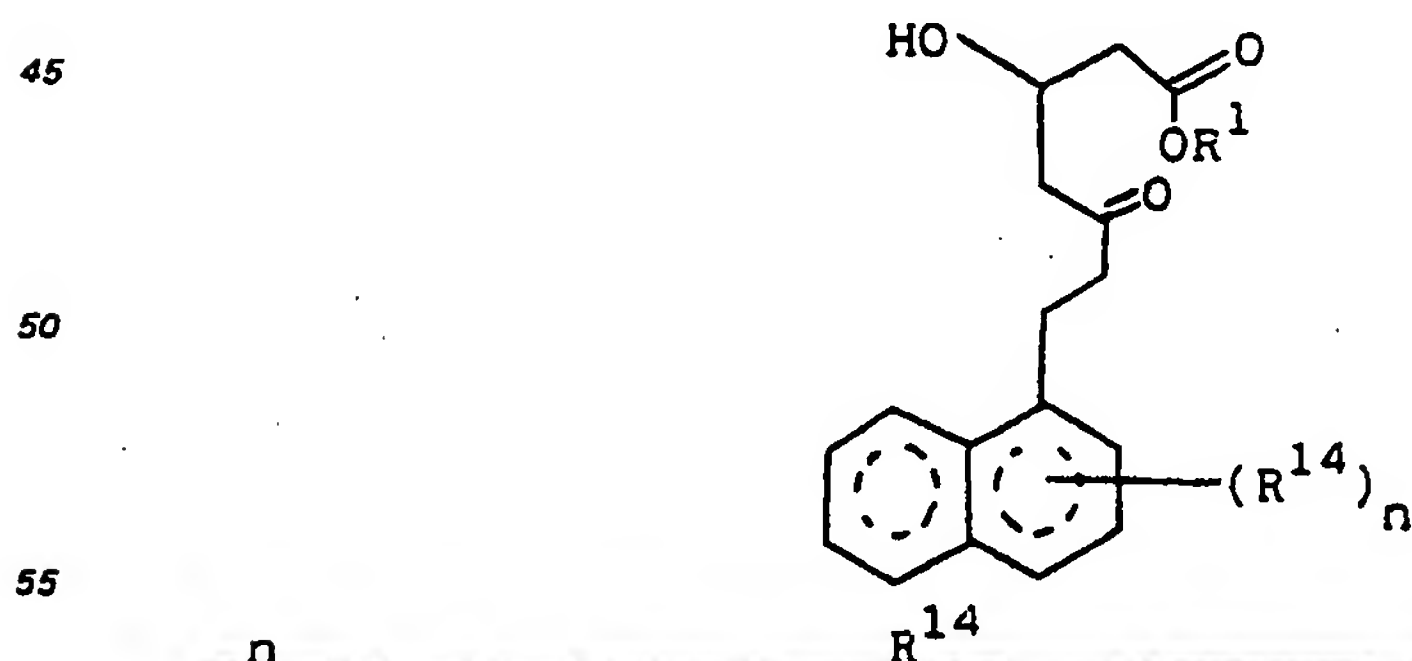
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5. Das Verfahren von Anspruch 3 zur Herstellung einer Verbindung, ausgewählt aus:



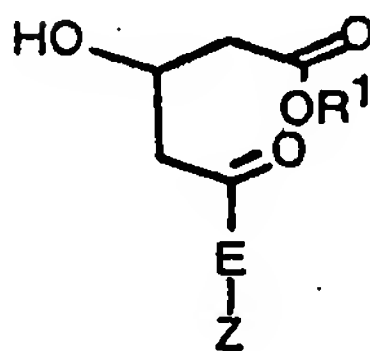
	R ¹⁰	R ¹¹	R ¹²
20	6-(4-Fluor-3-methylphenyl)-	2-Methyl	4-Methyl
	6-(4-Fluorphenyl)-	2-Chlor	4-Chlor
	6-(4-Chlorphenyl)-	2-Chlor	4-Chlor
25	6-(3,4-Dichlorphenyl)	2-Chlor	4-Chlor
	6-(4-Fluor-3-methylphenyl)	2-Chlor	4-Chlor
	6-(3,4-Dichlorphenyl)	2-Methyl	4-Methyl
30	5-(3,5-Dimethylphenyl)-	2-Chlor	4-Chlor
	6-(3,4-Dichlorphenyl)-	2-Methyl	5-Methyl
	6-(4-Fluorphenyl)	2-Methyl	4-Methyl
35	6-(4-Fluor-3-methylphenyl)-	2-Methyl	4-Chlor
	6-(4-Fluorbenzyloxy)	2-Chlor	4-Chlor
	6-(4-Fluor-3-methylphenyl)-	2-Chlor	4-Methyl

40 6. Das Verfahren von Anspruch 3 zur Herstellung einer Verbindung, ausgewählt aus:



n	R ¹⁴	
1	2-Methyl	Naphthyl
0	-	Naphthyl
60	2,6-Dimethyl	Naphthyl
1	2-Methyl	5,6,7,8-Tetrahydro-naphthyl

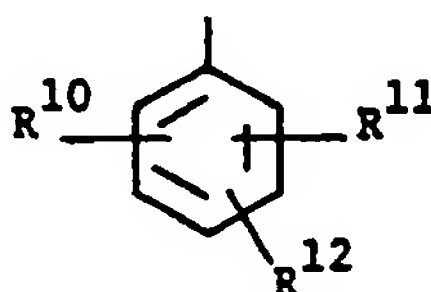
7. Ein Verfahren zur Herstellung einer Verbindung der Formel



10 worin:

- R¹) Wasserstoff,
 2) C₁-₄-Alkyl,
 3) 2,3-Dihydroxypropyl,
 4) ein Alkalimetallkation, oder
 5) ein Ammoniumkation der Formel N⁺R³R⁴R⁵R⁶ ist,
 wobei R³, R⁴, R⁵ und R⁶ unabhängig voneinander Wasserstoff oder C₁-₄-Alkyl sind, oder zwei Reste von R³, R⁴, R⁵ und R⁶ miteinander unter Bildung eines 5- oder 6-gliedrigen Heterocyclus mit dem Stickstoff, an den sie gebunden sind, verbunden sind;
 E —CH₂CH₂ oder —(CH₂)₃— ist; und
 Z

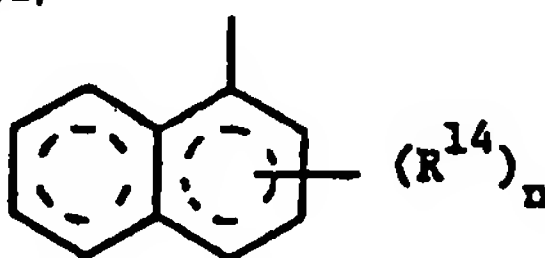
1)



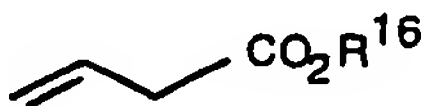
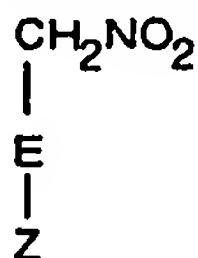
wobei R¹⁰, R¹¹ und R¹² unabhängig voneinander

- a) Wasserstoff,
 b) Halogen, wie Brom, Chlor oder Fluor,
 c) C₁-₄-Alkyl,
 d) Halogen-C₁-₄-Alkyl,
 e) Phenyl, das entweder unsubstituiert oder durch einen oder mehrere der Substituenten
 i) C₁-₄-Alkoxy,
 ii) C₁-₄-Alkyl,
 iii) C₂-₈-Alkanoyloxy,
 iv) Halogen-C₁-₄-Alkyl oder
 v) Halogen, substituiert ist, oder
 f) OR¹³, wobei R¹³
 i) Wasserstoff,
 ii) C₂-₈-Alkanoyl,
 iii) Benzoyl,
 iv) Phenyl,
 v) Halogenphenyl,
 vi) Phenyl-C₁-₃-alkyl, das entweder unsubstituiert oder durch einen oder mehrere Halogen-C₁-₄-Alkoxy-, C₁-₄-Alkyl- oder Halogen-C₁-₄-Alkylreste substituiert ist,
 vii) C₁-₈-Alkyl,
 viii) Zinnamyl,
 ix) Halogen-C₁-₄-alkyl,
 x) Allyl,
 xi) C₃-₈-Cycloalkyl-C₁-₃-alkyl, oder
 xii) Adamantyl-C₁-₃-alkyl ist, sind;

2)



wobei n 0—2 ist, und R¹⁴ Halogen oder C₁-₄-Alkyl ist; bedeutet; welches das Umsetzen der Verbindungen



unter Bildung der Verbindung der Strukturformel:



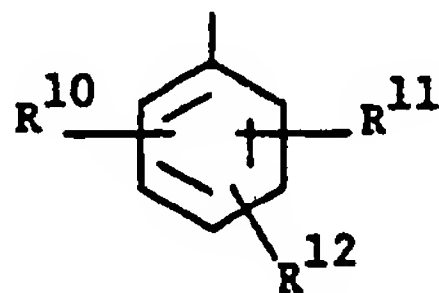
15 gefolgt von der katalytischen Reduktion unter Bildung der gewünschten Verbindung, worin R^1 R^{18} ist; gefolgt von der Behandlung mit Alkali unter Bildung des Produktes, worin R^1 ein Alkalimetallkation ist, gefolgt von der Ansäuerung unter Bildung der Verbindung, worin R^1 ein Wasserstoffion ist, umfaßt.

8. Das Verfahren von Anspruch 7, worin:

R^1 Wasserstoff, ein Alkalimetallkation oder ein Ammoniumkation ist;

20 $E-CH_2CH_2-$ ist; und
Z

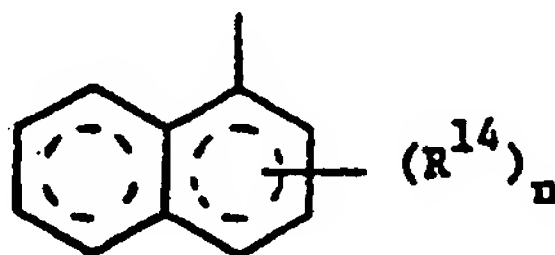
25 1)



wobei R^{10} , R^{11} und R^{12} unabhängig voneinander

- 30 a) Halogen,
b) C_{1-4} -alkyl,
c) Halogen- C_{1-4} -alkyl,
d) Phenyl mit 1 bis 3 Substituenten, ausgewählt aus Halogen, C_{1-4} -Alkyl oder C_{1-4} -Alkoxy, oder
e) OR^{13} , wobei R^{13}
35 i) Phenyl,
ii) Halogenphenyl oder
iii) Phenyl- C_{1-3} -alkyl ist, das entweder unsubstituiert oder durch einen oder mehrere Halogen-, C_{1-4} -Alkoxy-, C_{1-4} -Alkyl- oder Halogen- C_{1-4} -alkylreste substituiert ist, darstellen; oder

40 2)



45 wobei n 0, 1 oder 2 ist, und R^{14} Methyl ist, und das Ringsystem Naphthyl oder 5,6,7,8-Tetrahydronaphthyl ist, bedeutet.

50

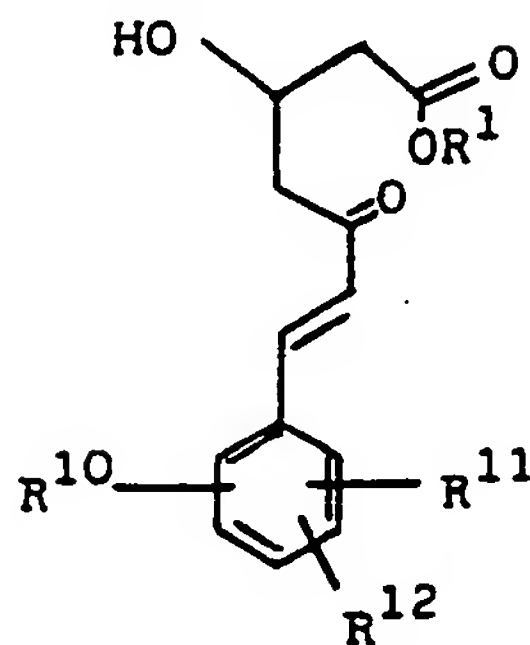
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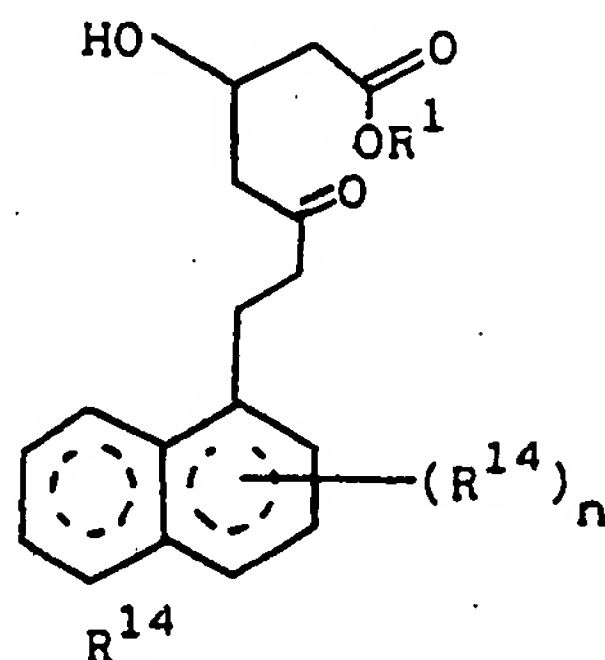
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9. Das Verfahren von Anspruch 8 zur Herstellung einer Verbindung, ausgewählt aus:



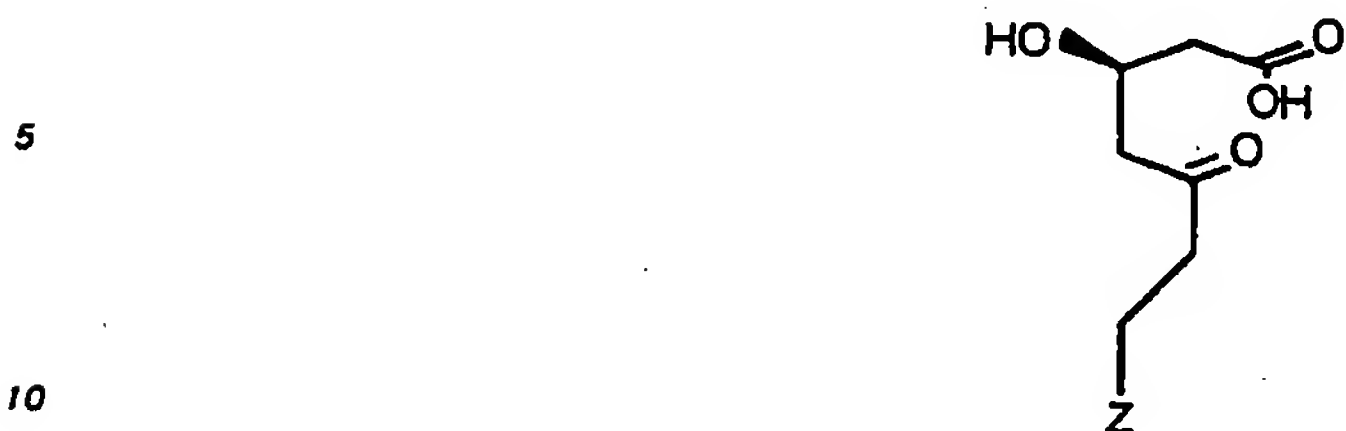
R^{10}	R^{11}	R^{12}
6-(4-Fluor-3-methylphenyl)-	2-Methyl	4-Methyl
6-(4-Fluorphenyl)-	2-Chlor	4-Chlor
6-(4-Chlorphenyl)-	2-Chlor	4-Chlor
6-(3,4-Dichlorphenyl)	2-Chlor	4-Chlor
6-(4-Fluor-3-methylphenyl)	2-Chlor	4-Chlor
6-(3,4-Dichlorphenyl)	2-Methyl	4-Methyl
6-(3,5-Dimethylphenyl)-	2-Chlor	4-Chlor
6-(3,4-Dichlorphenyl)-	2-Methyl	5-Methyl
6-(4-Fluorphenyl)	2-Methyl	4-Methyl
6-(4-Fluor-3-methylphenyl)-	2-Methyl	4-Chlor
6-(4-Fluorbenzyloxy)	2-Chlor	4-Chlor
6-(4-Fluor-3-methylphenyl)-	2-Chlor	4-Methyl

10. Das Verfahren von Anspruch 8 zur Herstellung einer Verbindung, ausgewählt aus:



n	R^{14}	
1	2-Methyl	Naphthyl
0	-	Naphthyl
2	2,6-Dimethyl	Naphthyl
1	2-Methyl	5,6,7,8-Tetrahydro-naphthyl

11. Ein Verfahren zur Herstellung einer Verbindung der Strukturformel:



worin Z wie in Anspruch 1 definiert ist,
welches das Behandeln einer Verbindung der Strukturformel:



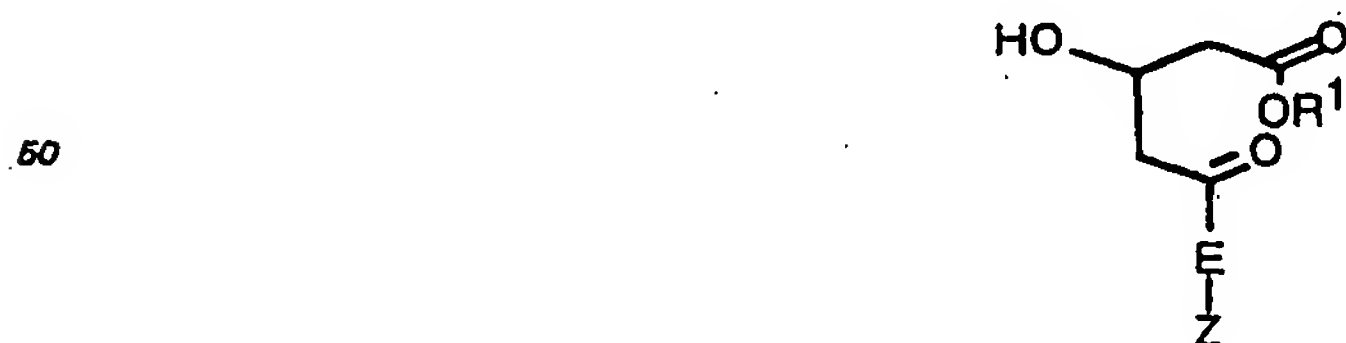
25 mit aktiviertem Mangandioxid unter Bildung der Verbindung der Strukturformel:



40 gefolgt von der Behandlung mit Tri-n-butylzinhydrid und Tetrakis(triphenylphosphin)palladium (O),
umfaßt.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL SE

45 1. Un composé répondant à la formule développée:



55 dans laquelle:

R¹ est

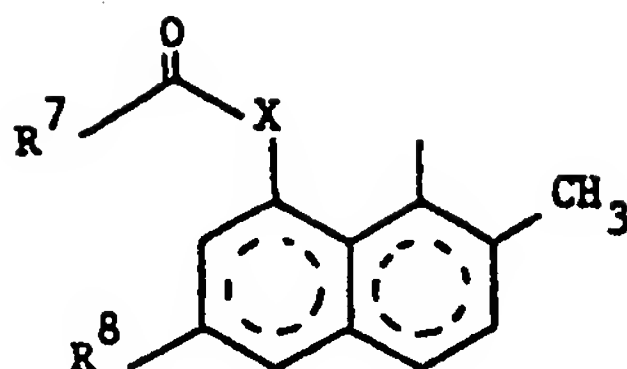
- 1) un hydrogène,
 - 2) un alkyle en C₁₋₄,
 - 3) un 2,3-dihydroxypropyle,
 - 4) un cation de métal alcalin ou
 - 5) un ammonium de formule N⁺R³R⁴R⁵R⁶ dans laquelle R³, R⁴, R⁵ et R⁶ sont indépendamment un
- 60 hydrogène ou un alkyle en C₁₋₄ ou deux de R³, R⁴, R⁵ et R⁶ sont réunis pour former un hétérocycle à 5 ou 6
chaînon avec l'azote auquel ils sont fixés;

E est —CH₂CH₂—, —CH=CH— ou —(CH₂)₃—; et

65 Z est

5

1)

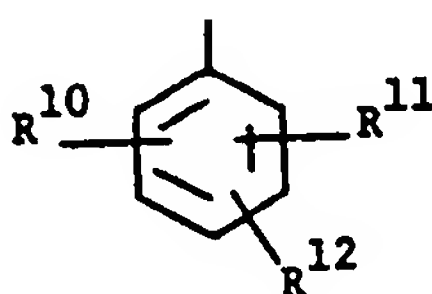


10

où les pointillés représentent tous les états d'oxydation possibles du système bicyclique;
X est —O— ou >NR⁹ où R⁹ est un hydrogène ou un alkyle en C₁₋₃;
R⁷ est un alkyle en C₂₋₈; et
R⁸ est un hydrogène ou —CH₃;

15

2)



20

où R¹⁰, R¹¹ et R¹² sont indépendamment

25

- a) un hydrogène,
- b) un halogène, tel que bromo, chloro ou fluoro,
- c) un alkyle en C₁₋₄,
- d) un halogénoalkyle en C₁₋₄,
- e) un phényle soit non substitué soit substitué par un ou plusieurs de

30

- i) alcoxy en C₁₋₄,
- ii) alkyle en C₁₋₄,
- iii) alcanoyloxy en C₂₋₈,
- iv) halogénoalkyle en C₁₋₄ ou
- v) halogéno, tel que bromo, chloro ou fluoro,
- f) OR¹³ où R¹³ est

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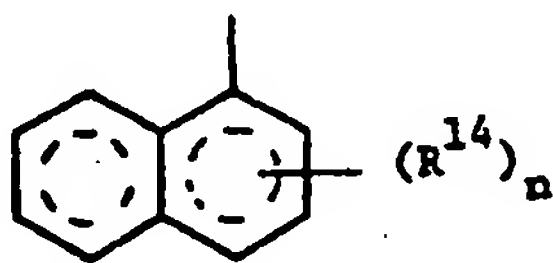
- i) un hydrogène,
- ii) un alcanoyloxy en C₂₋₈,
- iii) un benzoyloxy,
- iv) un phényle,
- v) un halogénophényle,

40

- vi) un phényl-alkyle en C₁₋₃ soit non substitué soit substitué par un ou plusieurs halogènes, alcoxy en C₁₋₄, alkyles en C₁₋₄ ou halogénoalkyles en C₁₋₄,
- vii) un alkyle en C₁₋₈,
- viii) un cinnamyle,
- ix) un halogénoalkyle en C₁₋₄,
- x) un allyle,
- xi) un cycloalkyl(C₃₋₆)-alkyle en C₁₋₃ ou
- xii) un adamantyl-alkyle en C₁₋₃,

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3)

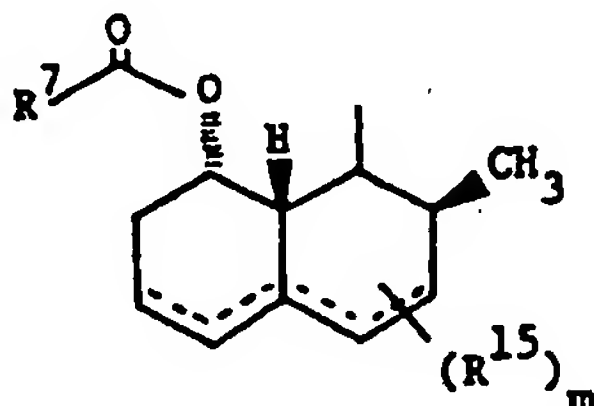


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où n est 0—2 et R¹⁴ est un halogéno ou un alkyle en C₁₋₄; et

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4)

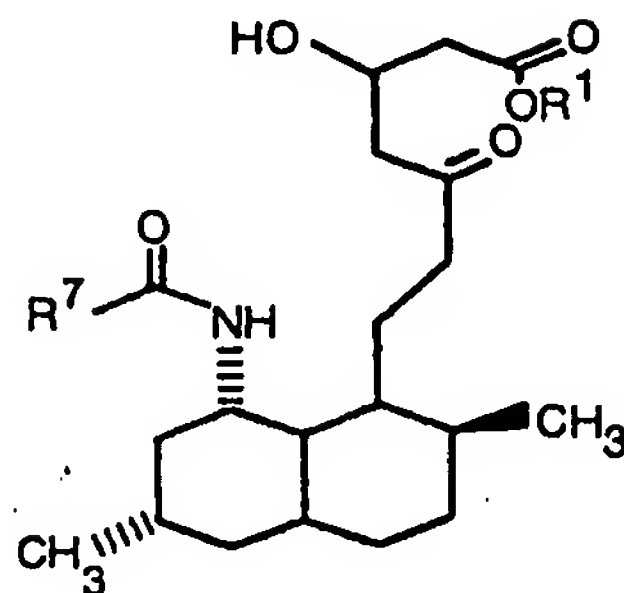


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où les pointillés représentent les doubles liaisons possibles, 0, 1 ou 2 doubles liaisons pouvant exister;
m représente 1, 2 ou 3; et
R¹⁵ est

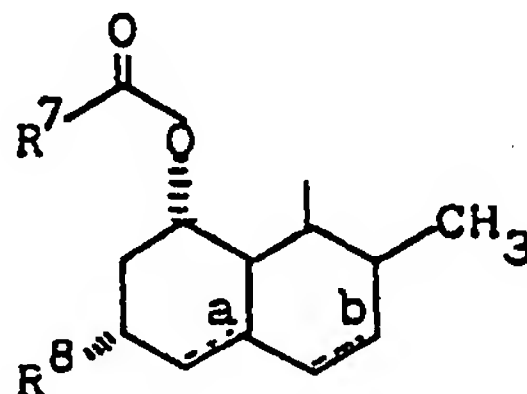
65

- 1) un méthyle,
 - 2) un hydroxy,
 - 3) un alcoxy en C₁₋₄,
 - 4) un oxo ou
 - 5) un halogéno.
2. Un composé répondant à la formule développée:

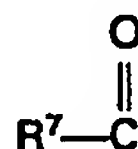


dans laquelle R¹ est un hydrogène, un cation de métal alcalin ou un cation ammonium et R⁷ est un 4-fluorobenzoyl, un 4-tert-butyl-benzoyl ou un 4-fluorophénylacétyl.

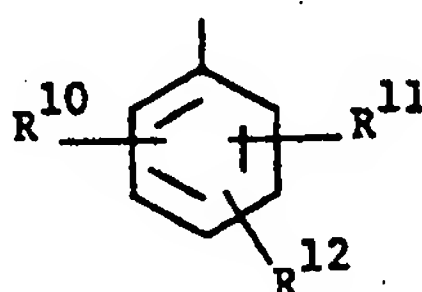
3. Le composé de la revendication 1 où:
 R¹ est un hydrogène, un cation de métal alcalin ou un cation ammonium;
 E est —CH=CH— ou —CH₂CH₂—; et
 Z est



dans laquelle

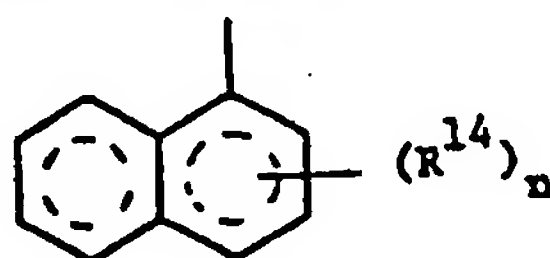


est un 2(S)-méthylbutyryl ou un 2-2-diméthylbutyryl;



où R¹⁰, R¹¹ et R¹² sont indépendamment:

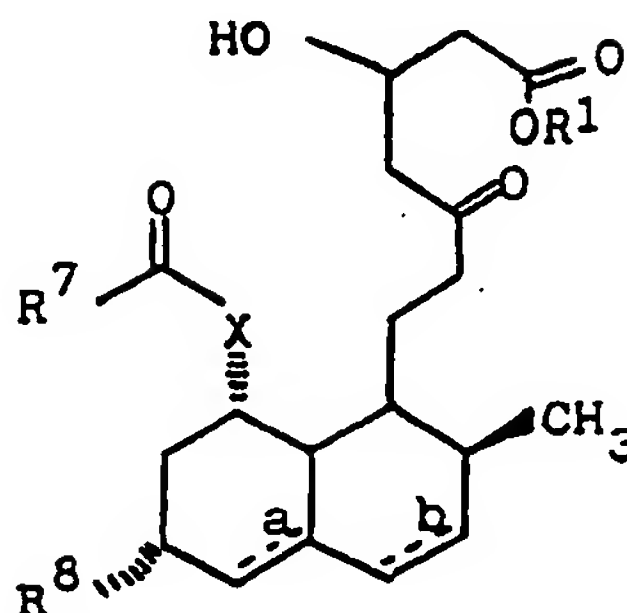
- a) un halogène,
- b) un alkyle en C₁₋₄,
- c) un halogénoalkyle en C₁₋₄,
- d) un phényle ayant 1 à 3 substituants choisis parmi halogéno, alkyle en C₁₋₄ ou alcoxy en C₁₋₄,
- e) OR¹³, où R¹³ est
 - i) un phényle,
 - ii) un halogénophényle, ou
 - iii) un phényl-alkyle en C₁₋₃ soit non substitué soit substitué par un ou plusieurs halogènes, alcoxy en C₁₋₄, alkyles en C₁₋₄ ou halogénoalkyles en C₁₋₄; ou



où n est 0, 1 ou 2 et R¹⁴ est un méthyle et le système cyclique est un naphthyle ou un 5,6,7,8-tétrahydronaphthyle.

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4. Le composé de la revendication 1 choisi parmi:



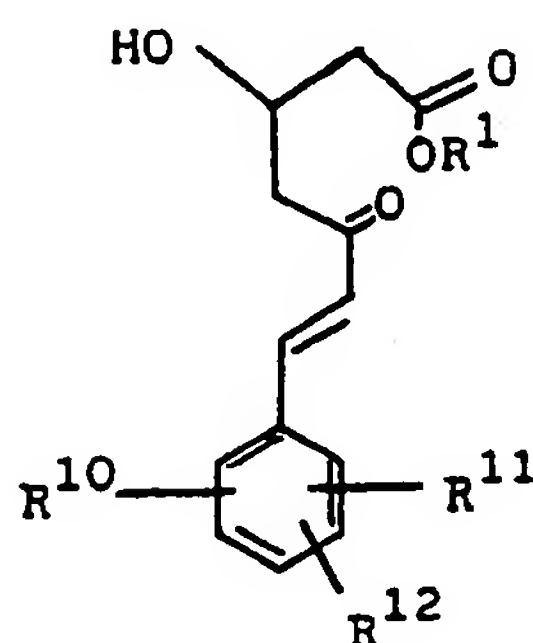
où R¹ est un hydrogène, un cation de métal alcalin ou un cation ammonium et où R⁷CO—, R⁸, X, a et b ont les significations suivantes:

R ⁷ -C(=O)-	R ⁸	x	a*	b
2(S)-méthylbutyryle	-CH ₃	O	simple	double
2(S)-méthylbutyryle	-CH ₃	O	simple	simple
2(R)-méthylbutyryle	-CH ₃	O	double	double
2,2-diméthylbutyryle	-CH ₃	O	double	double
2,2-diméthylbutyryle	-CH ₃	O	simple	double
2,2-diméthylbutyryle	-CH ₃	O	simple	simple
acétyle	-CH ₃	O	double	double
2(S)-méthylbutyryle	H	O	double	double
2(S)-méthylbutyryle	H	O	simple	simple
2,2-diméthylbutyryle	H	O	double	double
2,2-diméthylbutyryle	H	O	simple	simple
2,2-diméthylbutyryle	-CH ₃	NH	simple	simple
2-méthyl-2-éthylbutyryle	-CH ₃	NH	simple	simple
2-méthylbutyryle	-CH ₃	NH	simple	simple
acétyle	-CH ₃	NH	double	double
acétyle	-CH ₃	NCH ₃	simple	simple
2,2-diméthylbutyryle	-CH ₃	NCH ₃	simple	simple
2,2-diméthylbutyryle	-CH ₃	NH	double	double

* lorsque a = simple liaison, les cycles sont condensés en trans.

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5. Le composé de la revendication 3 choisi parmi



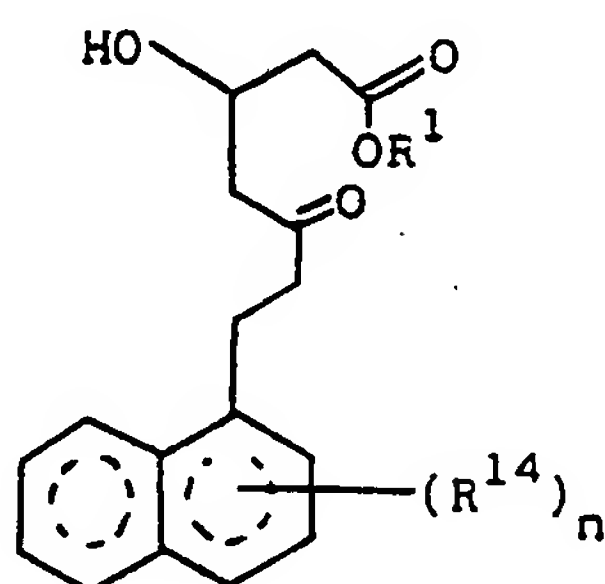
R¹⁰

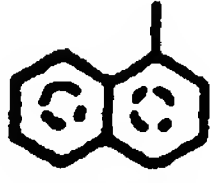
R¹¹

R¹²

20	6-(4-fluoro-3-méthylphényl)-	2-méthyl	4-méthyl
	6-(4-fluorophényl)-	2-chloro	4-chloro
	6-(4-chlorophényl)-	2-chloro	4-chloro
25	6-(3,4-dichlorophényl)-	2-chloro	4-chloro
	6-(4-fluoro-3-méthylphényl)-	2-chloro	4-chloro
	6-(3,4-dichlorophényl)-	2-méthyl	4-méthyl
30	6-(3,5-diméthylphényl)-	2-chloro	4-chloro
	6-(3,4-dichlorophényl)-	2-méthyl	5-méthyl
	6-(4-fluorophényl)-	2-méthyl	4-méthyl
35	6-(4-fluoro-3-méthylphényl)-	2-méthyl	4-chloro
	6-(4-fluorobenzoyloxy)-	2-chloro	4-chloro
	6-(4-fluoro-3-méthylphényl)-	2-chloro	4-méthyl

6. Le composé de la revendication 3 choisi parmi:



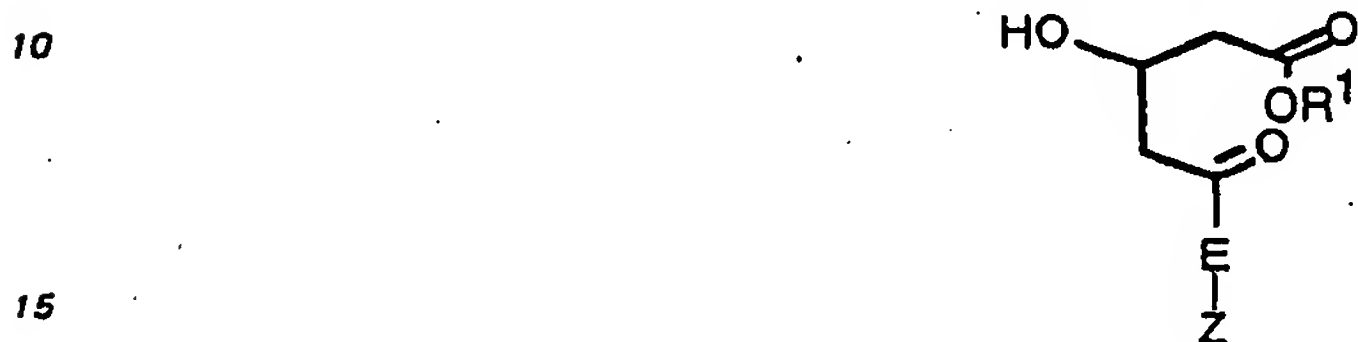
55	n	R¹⁴	
	1	2-méthyl	naphtyle
60	0	-	naphtyle
	2	2,6-diméthyl	naphtyle
65	1	2-méthyl	5,6,7,8-tétrahydronaphtyle

7. Une composition pharmaceutique antihypercholestérolémiant comprenant un support pharmaceutique et une quantité antihypercholestérolémiant efficace d'un composé comme revendiqué dans la revendication 1 ou 2.

8. La composition de la revendication 7, dans laquelle le composé antihypercholestérolémiant est comme revendiqué dans la revendication 3.

9. La composition de la revendication 8, dans laquelle le composé antihypercholestérolémiant est comme revendiqué dans les revendications 4, 5 ou 6.

10. Un procédé pour la préparation d'un composé répondant à la formule développée:



dans laquelle R¹, E et Z ont les significations de R¹, E et Z 1), 2) et 3) dans la revendication 1, qui comprend le traitement d'un composé répondant à la formule développée:



30 dans laquelle R¹⁶ est un alkyle en C₁-₄, avec un agent oxydant pour produire le composé de formule développée:



suivi d'une désilylation pour produire le composé de formule développée:



suivie d'un traitement avec un alcali pour former le produit dans lequel R¹⁶ est un cation de métal alcalin, suivi d'une acidification pour produire le composé dans lequel R¹⁶ est un ion hydrogène.

55 Revendications pour l'Etat contractant: AT

1. Un procédé pour la préparation d'un composé répondant à la formule développée:



65 dans laquelle:

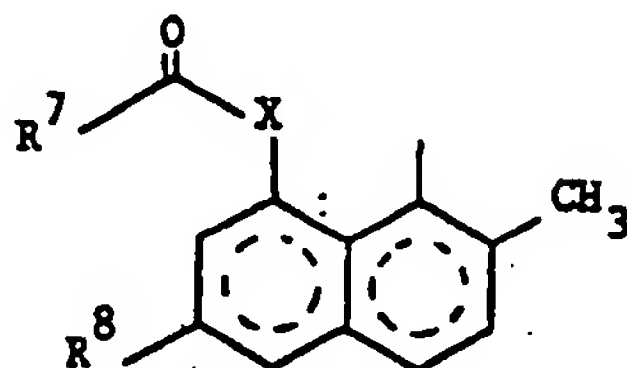
R¹ est

- 1) un hydrogène,
- 2) un alkyle en C₁₋₄,
- 3) un 2,3-dihydroxypropyle,
- 4) un cation de métal alcalin ou
- 5) un ammonium de formule N⁺R³R⁴R⁵R⁶ dans laquelle R³, R⁴, R⁵ et R⁶ sont indépendamment un hydrogène ou un alkyle en C₁₋₄ ou deux de R³, R⁴, R⁵ et R⁶ sont réunis pour former un hétérocycle à 5 ou 6 chaînons avec l'azote auquel ils sont fixés;

E est —CH₂CH₂—, —CH=CH— ou —(CH₂)₃—; et

Z est

1)



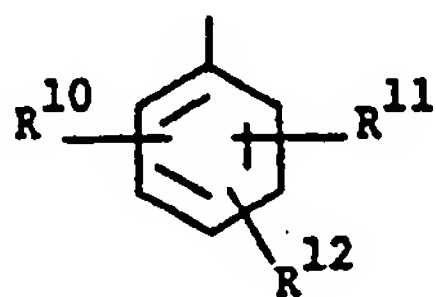
où les pointillés représentent tous les états d'oxydation possibles du système bicyclique;

X est —O— ou >NR⁹ où R⁹ est un hydrogène ou un alkyle en C₁₋₃;

R⁷ est un alkyle en C₂₋₈; et

R₈ est un hydrogène ou —CH₃;

2)



où R¹⁰, R¹¹ et R¹² sont indépendamment

a) un hydrogène,

b) un halogène, tel que bromo, chloro ou fluoro,

c) un alkyle en C₁₋₄,

d) un halogénoalkyle en C₁₋₄,

e) un phényle soit non substitué soit substitué par un ou plusieurs de

i) alcoxy en C₁₋₄,

ii) alkyle en C₁₋₄,

iii) alcanoyloxy en C₂₋₈,

iv) halogénoalkyle en C₁₋₄ ou

v) halogéno,

f) OR¹³ où R¹³ est

i) un hydrogène,

ii) un alcanoyloxy en C₂₋₈,

iii) un benzoyle,

iv) un phényle,

v) un halogénophényle,

vi) un phényl-alkyle en C₁₋₃ soit non substitué soit substitué par un ou plusieurs halogènes, alcoxy en C₁₋₄, alkyles en C₁₋₄ ou halogénoalkyles en C₁₋₄,

vii) un alkyle en C₁₋₉,

viii) un cinnamyle,

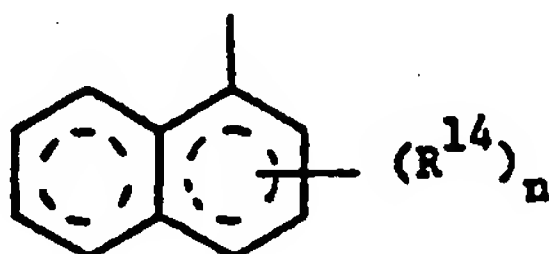
ix) un halogénoalkyle en C₁₋₄,

x) un allyle,

xi) un cycloalkyl(C₃₋₆)-alkyle en C₁₋₃,

xii) un adamantyl-alkyle en C₁₋₃,

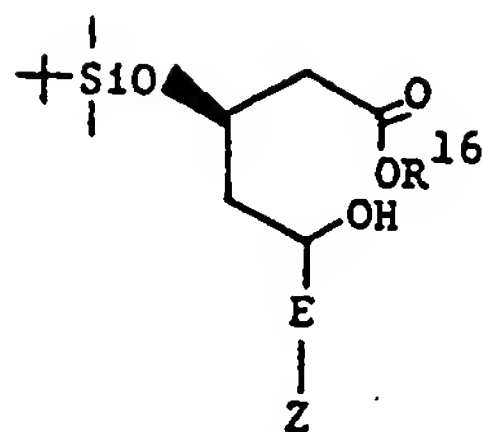
3)



où n est 0—2 et R¹⁴ est un halogéno ou alkyle en C₁₋₄, qui comprend le traitement d'un composé répondant à la formule développée:

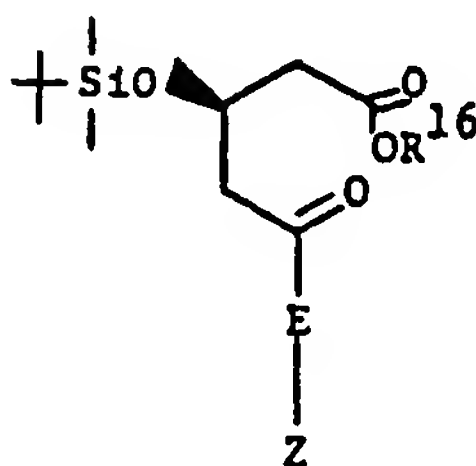
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10 dans laquelle R^{16} est un alkyle en C_{1-4} avec un agent oxydant pour produire le composé de formule développée:

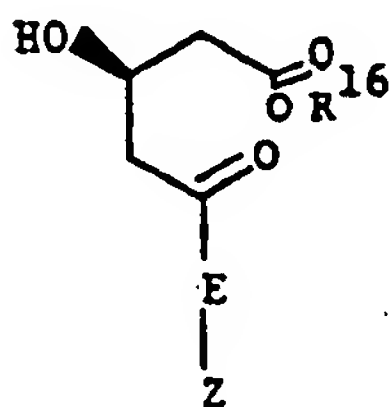
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suivi d'une désilylation pour produire le composé de formule développée:

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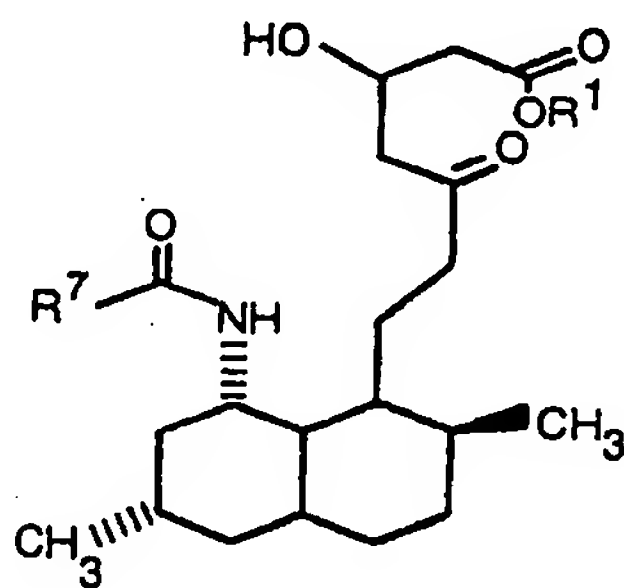


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suivie d'un traitement avec un alcali pour former le produit dans lequel R^{16} est un cation de métal alcalin, suivi d'une acidification pour produire le composé dans lequel R^{16} est un ion hydrogène.

35 2. Un procédé pour la préparation d'un composé répondant à la formule développée:

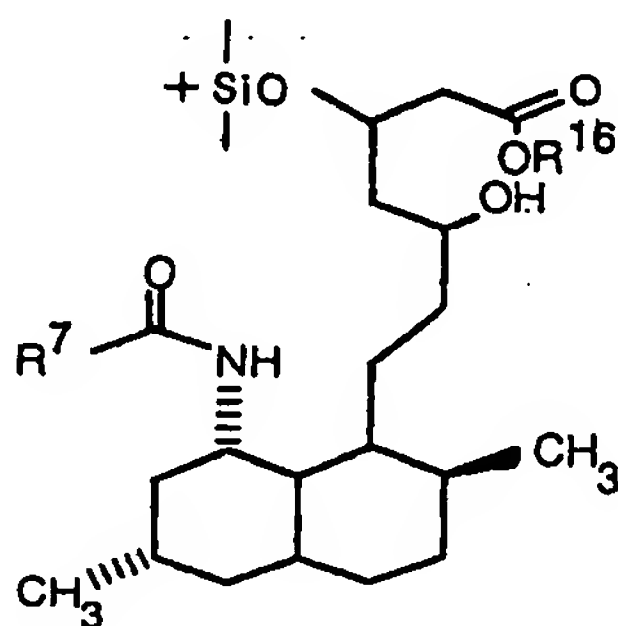
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50 dans laquelle R^1 est un hydrogène, un cation de métal alcalin ou un cation ammonium et où R^7 est un 4-fluorobenzoyl, un 4-tert-butylbenzoyl ou un 4-fluorophénylacétyl, qui comprend le traitement d'un composé répondant à la formule développée:

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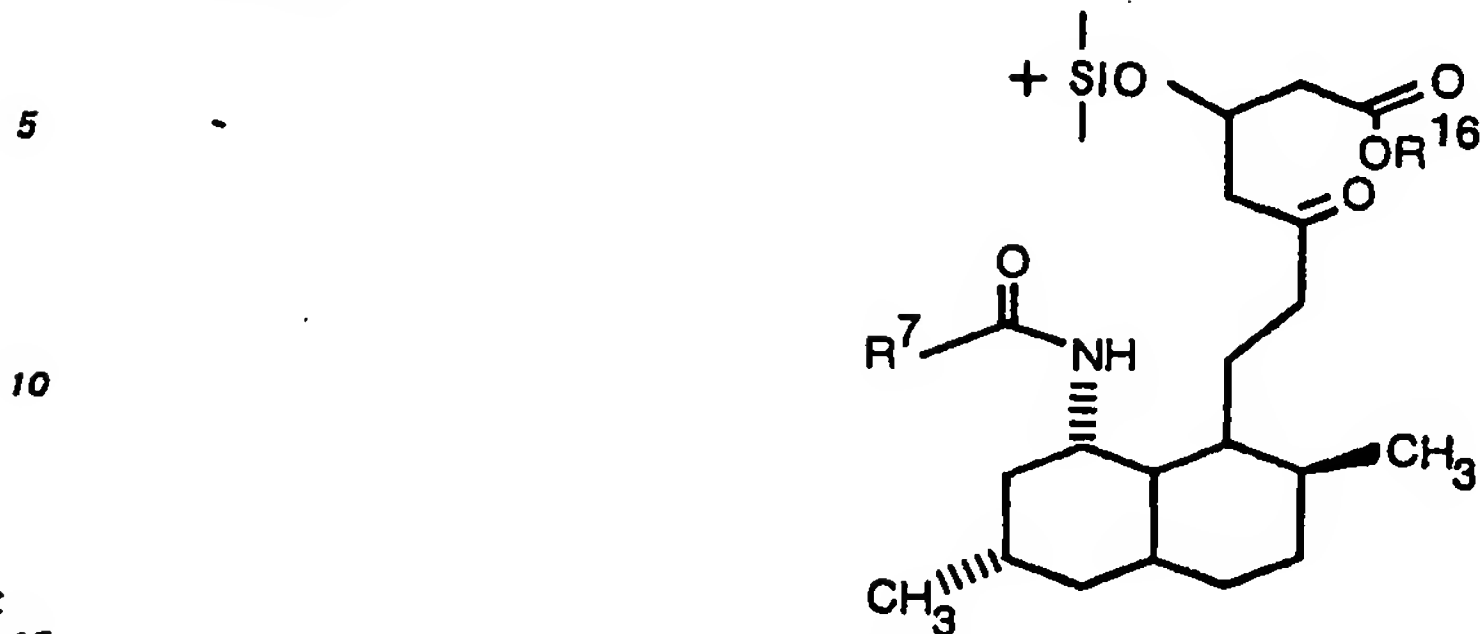


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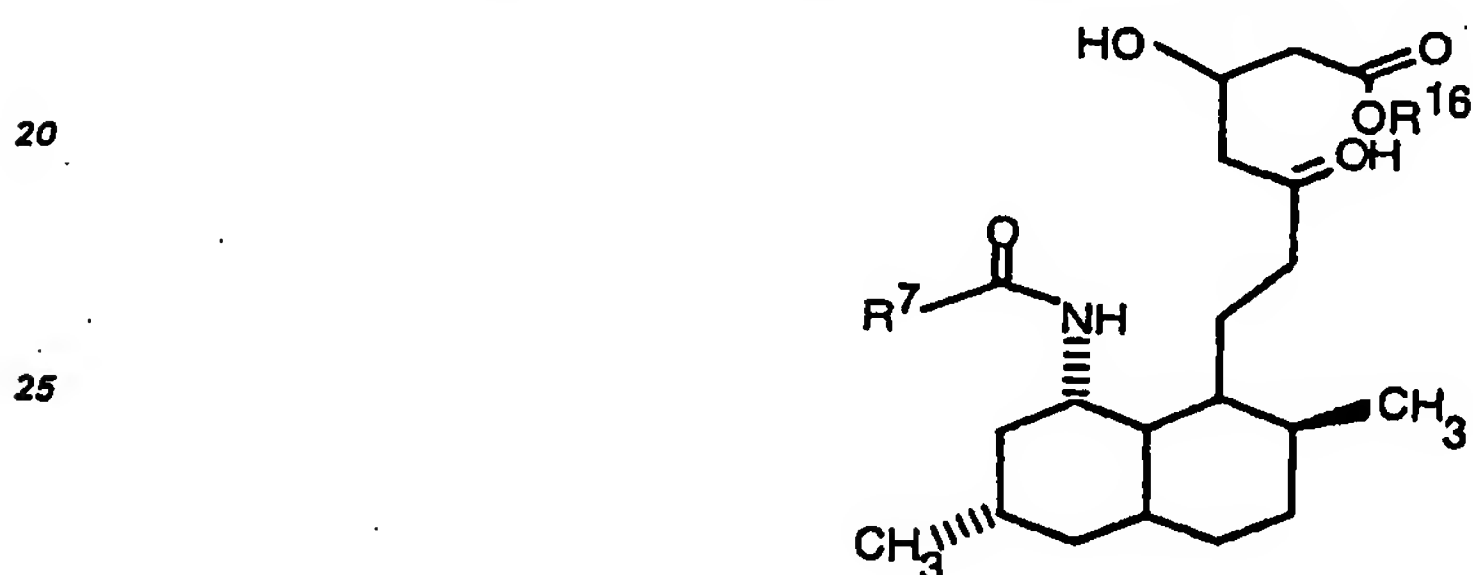
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dans laquelle R^{16} est un alkyle en C_{1-4} , avec un agent oxydant pour produire le composé de formule développée:



suivi d'une désilylation pour produire le composé de formule développée:



30 suivie d'un traitement avec un alcali pour produire le composé dans lequel R^{16} est un cation de métal alcalin, suivi d'une acidification pour produire le composé dans lequel R^{16} est un ion hydrogène.

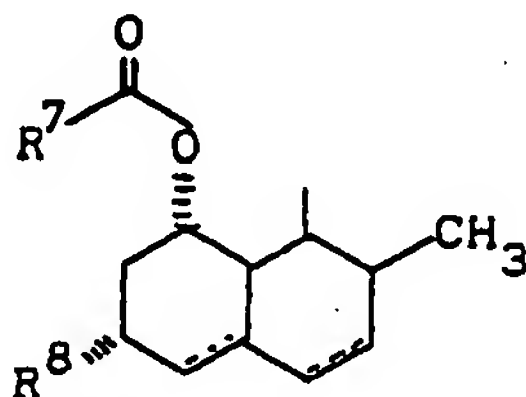
3. Le procédé de la revendication 1 dans lequel:

R^1 est un hydrogène, un cation de métal alcalin ou un cation ammonium;

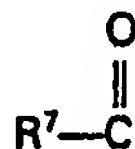
E est $-\text{CH}=\text{CH}-$ ou $-\text{CH}_2\text{CH}_2-$; et

Z est

40 1)

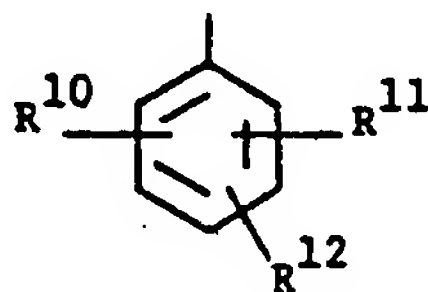


45 dans laquelle



50 est un 2(S)-méthylbutyryle ou un 2-2-diméthylbutyryle;

55 2)



où R^{10} , R^{11} et R^{12} sont indépendamment:

a) un halogène,

b) un alkyle en C_{1-4} ,

c) un halogénoalkyle en C_{1-4} ,

d) un phényle ayant 1 à 3 substituants choisis parmi halogéno, alkyle en C_{1-4} ou alcoxy en C_{1-4} ,

e) OR^{13} , où R^{13} est

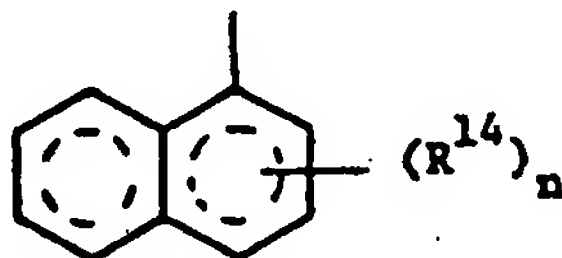
i) un phényle,

ii) un halogénophényle, ou

iii) un phényl-alkyle en C₁₋₃ soit non substitué soit substitué par un ou plusieurs halogènes, alcoxy en C₁₋₄, alkyles en C₁₋₄ ou halogénoalkyles en C₁₋₄; ou

5

3)



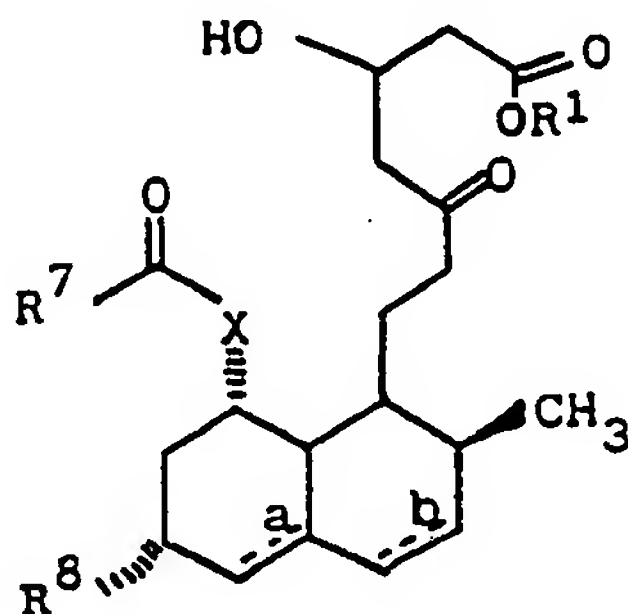
10 où n est 0, 1 ou 2 et R¹⁴ est un méthyle, et le système cyclique est un naphtalène ou un 5,6,7,8-tétrahydronaphtalène.

4. Le procédé de la revendication 1 pour la préparation d'un composé choisi parmi:

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où R¹ est un hydrogène, un cation de métal alcalin ou un cation ammonium et R⁷CO—, R⁸, X, a et b ont les significations suivantes:

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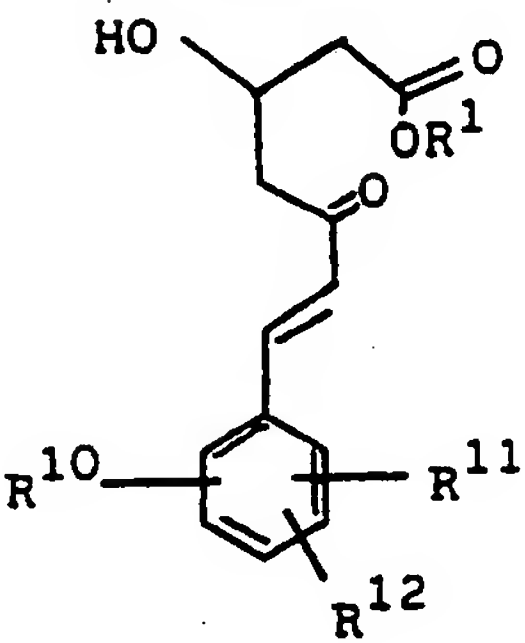
R ⁷ -C(=O)-	R ⁸	x	a*	b
2(S)-méthylbutyryle	-CH ₃	0	simple	double
2(S)-méthylbutyryle	-CH ₃	0	simple	simple
2(R)-méthylbutyryle	-CH ₃	0	double	double
2,2-diméthylbutyryle	-CH ₃	0	double	double
2,2-diméthylbutyryle	-CH ₃	0	simple	double
2,2-diméthylbutyryle	-CH ₃	0	simple	simple
acétyle	-CH ₃	0	double	double
2(S)-méthylbutyryle	H	0	double	double
2(S)-méthylbutyryle	H	0	simple	simple
2,2-diméthylbutyryle	H	0	double	double
2,2-diméthylbutyryle	H	0	simple	simple
2,2-diméthylbutyryle	-CH ₃	NH	simple	simple
2-méthyl-2-éthylbutyryle	-CH ₃	NH	simple	simple
2-méthylbutyryle	-CH ₃	NH	simple	simple
acétyle	-CH ₃	NH	double	double
acétyle	-CH ₃	NCH ₃	simple	simple
2,2-diméthylbutyryle	-CH ₃	NCH ₃	simple	simple
2,2-diméthylbutyryle	-CH ₃	NH	double	double

* lorsque a = simple liaison, les cycles sont condensés en trans.

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5. Le procédé selon la revendication 3 pour la préparation d'un composé choisi parmi



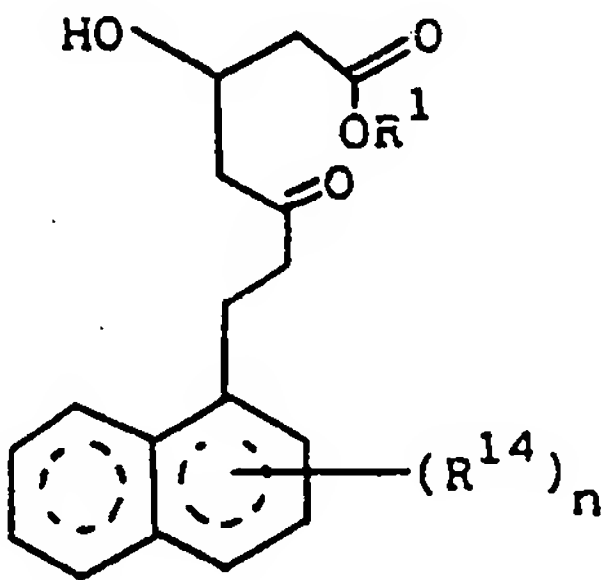
R¹⁰

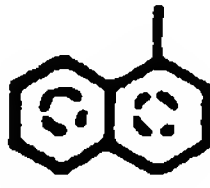
R¹¹

R¹²

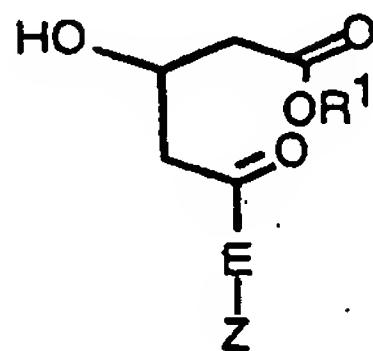
6-(4-fluoro-3-méthylphényl)-	2-méthyl	4-méthyl
6-(4-fluorophényl)-	2-chloro	4-chloro
6-(4-chlorophényl)-	2-chloro	4-chloro
6-(3,4-dichlorophényl)-	2-chloro	4-chloro
6-(4-fluoro-3-méthylphényl)-	2-chloro	4-chloro
6-(3,4-dichlorophényl)-	2-méthyl	4-méthyl
6-(3,5-diméthylphényl)-	2-chloro	4-chloro
6-(3,4-dichlorophényl)-	2-méthyl	5-méthyl
6-(4-fluorophényl)-	2-méthyl	4-méthyl
6-(4-fluoro-3-méthylphényl)-	2-méthyl	4-chloro
6-(4-fluorobenzoyloxy)-	2-chloro	4-chloro
6-(4-fluoro-3-méthylphényl)-	2-chloro	4-méthyl

6. Le procédé de la revendication 3 pour la préparation d'un composé choisi parmi:



n	R¹⁴	
1	2-méthyl	naphtyle
0	-	naphtyle
2	2,6-diméthyl	naphtyle
1	2-méthyl	5,6,7,8-tétrahydronaphtyle

7. Un procédé pour la préparation d'un composé de formule:

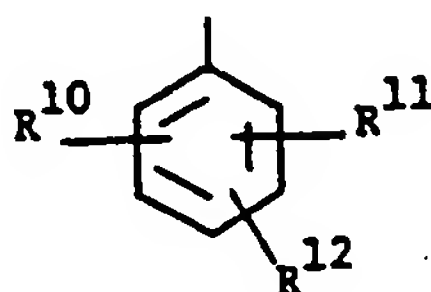


10 dans laquelle

R¹ est

- 1) un hydrogène,
- 2) un alkyle en C₁₋₄,
- 3) un 2,3-dihydroxypropyle,
- 15 4) un cation de métal alcalin ou
- 5) un ammonium de formule N⁺R³R⁴R⁵R⁶ dans laquelle R³, R⁴, R⁵ et R⁶ sont indépendamment un hydrogène ou un alkyle en C₁₋₄ ou deux de R³, R⁴, R⁵ et R⁶ sont réunis pour former un hétérocycle à 5 ou 6 chaînons avec l'azote auquel ils sont fixés;
- E est —CH₂CH₂—, ou —(CH₂)₃—; et
- 20 Z est

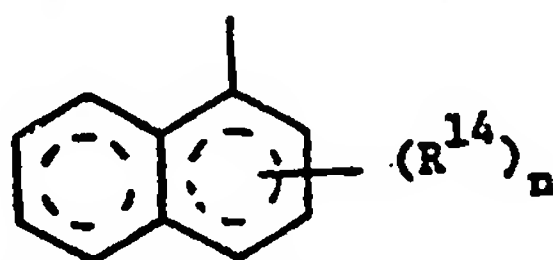
1)



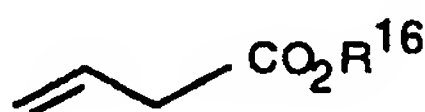
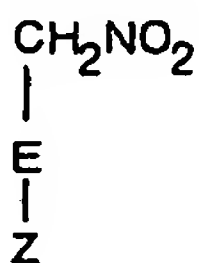
où R¹⁰, R¹¹ et R¹² sont indépendamment

- a) un hydrogène,
- 30 b) un halogène, tel que bromo, chloro ou fluoro,
- c) un alkyle en C₁₋₄,
- d) un halogénoalkyle en C₁₋₄,
- e) un phényle soit non substitué soit substitué par un ou plusieurs de
 - i) alcoxy en C₁₋₄,
 - 35 ii) alkyle en C₁₋₄,
 - iii) alcanoyloxy en C₂₋₈,
 - iv) halogénoalkyle en C₁₋₄ ou
 - v) halogéno,
 - f) OR¹³ où R¹³ est
 - 40 i) un hydrogène,
 - ii) un alcanoyloxy en C₂₋₈,
 - iii) un benzoyle,
 - iv) un phényle,
 - v) un halogénophényle,
 - 45 vi) un phényl-alkyle en C₁₋₃ soit non substitué soit substitué par un ou plusieurs halogènes, alcoxy
- en C₁₋₄, alkyles en C₁₋₄ ou halogénoalkyles en C₁₋₄,
- vii) un alkyle en C₁₋₉,
- viii) un cinnamyle,
- 50 ix) un halogénoalkyle en C₁₋₄,
- x) un allyle,
- xi) un cycloalkyl(C₃₋₆)-alkyle en C₁₋₃ ou
- xii) un adamantyl-alkyle en C₁₋₃,

2)



où n est 0—2 et R¹⁴ est un halogéno ou un alkyle en C₁₋₄ qui comprend la réaction des composés:



pour produire le composé de formule développée:



15 suivie d'une réduction catalytique pour produire le composé désiré dans lequel R^1 est R^{16} ; suivie d'un traitement avec un alcali pour former le produit dans lequel R^1 est un cation de métal alcalin, suivi d'une acidification pour produire le composé dans lequel R^1 est un ion hydrogène.

8. Le procédé de la revendication 7, dans lequel:

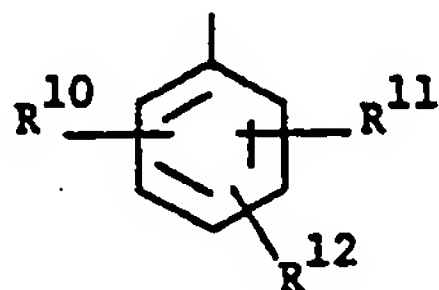
R^1 est un hydrogène, un cation de métal alcalin ou un cation ammonium;

20 E est $-\text{CH}_2\text{CH}_2-$; et

Z est

1)

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où R^{10} , R^{11} et R^{12} sont indépendamment:

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a) un halogène,

b) un alkyle en C_{1-4} ,

c) un halogénoalkyle en C_{1-4} ,

d) un phényle avec 1 à 3 substituants choisis parmi halogéno, alkyle en C_{1-4} ou alcoxy en C_{1-4} ,

e) OR^{13} , où R^{13} est

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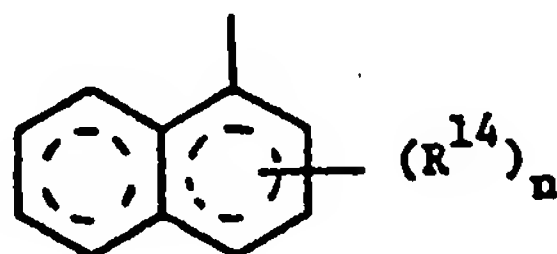
i) un phényle,

ii) un halogénophényle, ou

iii) un phényl-alkyle en C_{1-3} soit non substitué soit substitué par un ou plusieurs halogènes, alcoxy en C_{1-4} , alkyles en C_{1-4} ou halogénoalkyles en C_{1-4} ; ou

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2)



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où n est 0, 1 ou 2 et R^{14} est un méthyle et le système cyclique est un naphthalène ou un 5,6,7,8-tétrahydronaphthalène.

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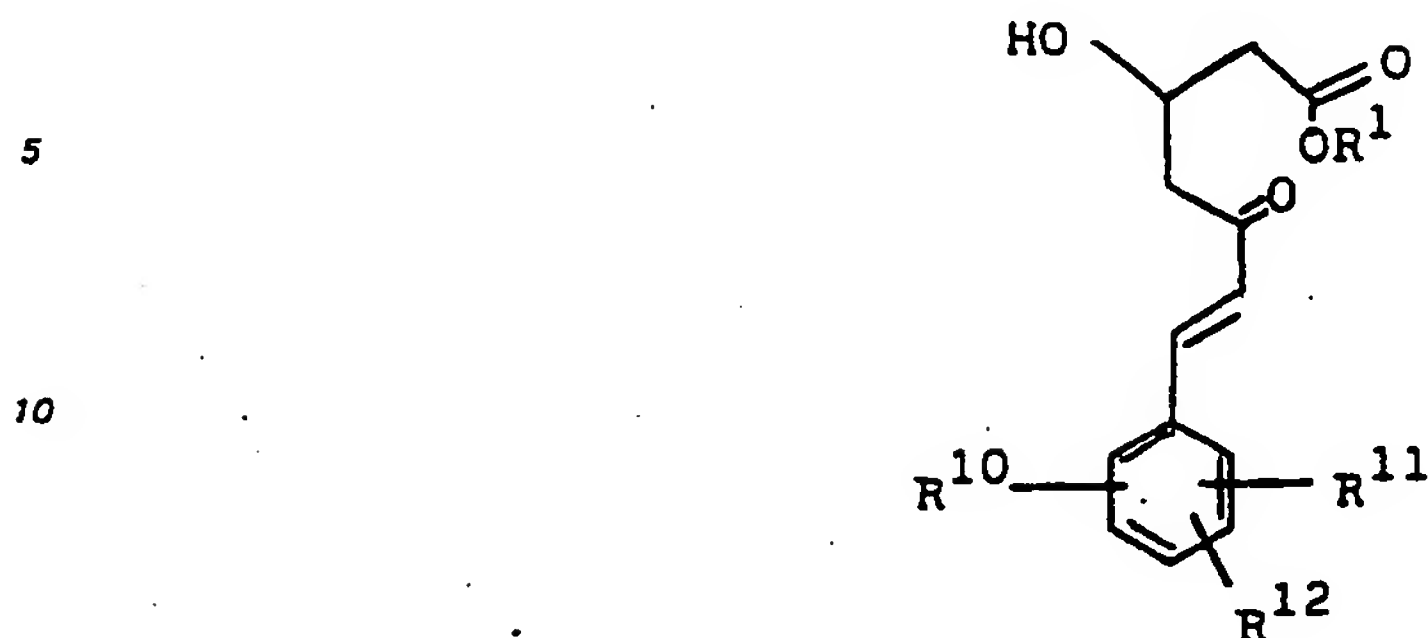
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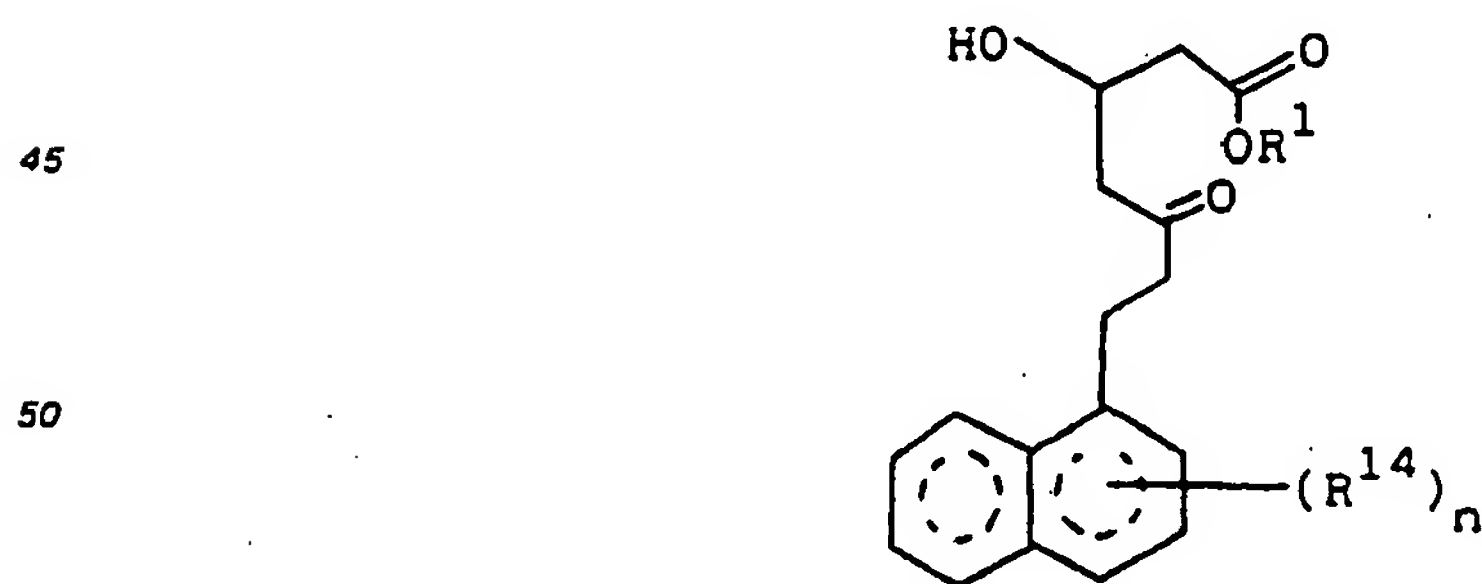
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9. Le procédé de la revendication 8 pour la préparation d'un composé choisi parmi



	R ¹⁰	R ¹¹	R ¹²
20	6-(4-fluoro-3-méthylphényl)-	2-méthyl	4-méthyl
	6-(4-fluorophényl)-	2-chloro	4-chloro
	6-(4-chlorophényl)-	2-chloro	4-chloro
25	6-(3,4-dichlorophényl)-	2-chloro	4-chloro
	6-(4-fluoro-3-méthylphényl)-	2-chloro	4-chloro
	6-(3,4-dichlorophényl)-	2-méthyl	4-méthyl
	6-(3,5-diméthylphényl)-	2-chloro	4-chloro
30	6-(3,4-dichlorophényl)-	2-méthyl	5-méthyl
	6-(4-fluorophényl)-	2-méthyl	4-méthyl
	6-(4-fluoro-3-méthylphényl)-	2-méthyl	4-chloro
35	6-(4-fluorobenzoyloxy)-	2-chloro	4-chloro
	6-(4-fluoro-3-méthylphényl)-	2-chloro	4-méthyl

40 10. Le procédé de la revendication 8 pour la préparation d'un composé choisi parmi:

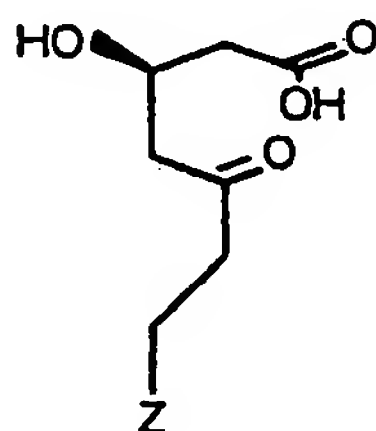


n	R ¹⁴	
1	2-méthyl	naphtyle
0	-	naphtyle
2	2,6-diméthyl	naphtyle
1	2-méthyl	5,6,7,8-tétrahydronaphtyle

11. Un procédé pour la préparation d'un composé répondant à la formule développée:

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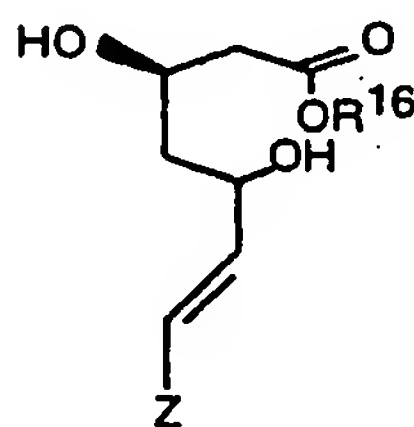
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dans laquelle Z est comme défini dans la revendication 1, qui comprend le traitement d'un composé de formule développée:

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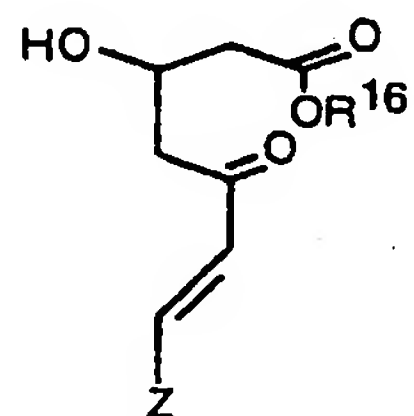
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avec du dioxyde de manganèse activé pour produire le composé de formule développée:

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35 suivi d'un traitement avec l'hydruire de tri-n-butylétain et le tétrakis(triphénylphosphine)palladium(0).

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